# Appendix A

## In Depth Review[A1] Of:

## "Pervasive Developmental Disorders in Montreal, Quebec, Canada: Prevalence and Links With Immunizations,"

**by Eric Fombonne, Rita Zakarian, Andrew Bennett, Linyan Meng & Diane McLean-Heywood**

***Pediatrics***. 2006 July; **118**(1): e139-e150

**A1** 27 September 2006 Review by CoMeD's Science Advisor without That Review's Appendices

## AN IN-DEPTH ASSESSMENT OF:

"**Pervasive Developmental Disorders in Montreal, Quebec, Canada: Prevalence and Links With Immunizations**," by Eric Fombonne, Rita Zakarian, Andrew Bennett, Linyan Meng, and Diane McLean-Heywood as published in ***Pediatrics***. 2006 July; **118**(1): e139-e150 (doi:10.1542/peds.2005-2993).

"ABSTRACT

**BACKGROUND.** The prevalence of pervasive developmental disorders has increased in recent years. Links with the measles component of the measles-mumps-rubella vaccine and the cumulative exposure to thimerosal through other vaccines have been postulated.

**OBJECTIVES.** The purpose of this work was to estimate the pervasive developmental disorder prevalence in Montreal, Canada, in cohorts born from 1987 to 1998 and evaluate the relationship of trends in pervasive developmental disorder rates with: (1) changes in cumulative exposure to ethylmercury (thimerosal) occurring through modifications in the immunization schedule of young children and (2) trends in measles-mumps-rubella vaccination use rates and the introduction of a 2–measles-mumps-rubella dosing schedule during the study period.

**METHODS.** We surveyed 27749 children born from 1987 to 1998 attending 55 schools from the largest Anglophone school board. Children with pervasive developmental disorders were identified by a special needs team. The cumulative exposure by age 2 years to thimerosal was calculated for 1987–1998 birth cohorts. Ethylmercury exposure ranged from medium (100–125 μg) from 1987 to 1991 to high (200–225 μg) from 1992 to 1995 to nil from 1996 onwards when thimerosal was entirely discontinued."

The first problem this reviewer has is that the authors' use of the word "*prevalence*" in the title, and elsewhere, is misleading because all that the authors' data allows the authors to compute is the apparent *incidence* rates by grade for a portion of a minority population (the English-speaking students attending a given set of schools) in a province, Quebec, where the majority of the people are French-speaking.

Second, the researcher's "*to nil from 1996 onwards when thimerosal was entirely discontinued*" statement is at odds with the facts.

This is the case because the only licensed hepatitis B vaccines were Thimerosal-preserved vaccines until 2001 and these Thimerosal-preserved hepatitis B vaccines, licensed in the 1980s, were given to many children in Quebec in the 1990s – *at birth*, 1 dose followed by 1 or 2 others before age two and/or, *in grade school*, 1 to 2 doses, in the period from 1996 to 1998. [**Note:** In Canada, GSK's Energix-B (hepatitis B formulation) was changed to a reduced-Thimerosal formulation on 20 December 2001. Similarly, Merck Frosst Canada & Co.'s Recombivax HB was licensed as a "preservative-free" vaccine formulation on 16 March 2001. In addition, anecdotal teacher reports have placed the Quebec immunization rate for hepatitis B as more than 25% for school-age children. Furthermore, one of the 1996 Canadian immunization "goals" for hepatitis B was universal immunization by 1997 (***Canadian Communicable Disease Report*** (***CCDR***), Volume **24**-S4, May 1997, online at: http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/97vol23/23s4/index.html, last visited on 4 August 2006) clearly indicating that the hepatitis B vaccine was being widely used by 1996.]

In addition, Thimerosal-preserved gamma-globulin drugs and influenza vaccines may have been administered to some pregnant Canadian women during this period.

*In some cases*, a Thimerosal-preserved influenza vaccine may also have been administered to some children in "high risk groups" as young as 6 months of age and annually thereafter.

Thus, *on average*, such children, *if given an annual flu shot from birth to age 16 starting in the early 1990s*, may have received up to 150 µg of mercury from Thimerosal-preserved flu-shots by 1998 when they would be in Grade 7, 8 or 9.

Further, the study design seems to fail to consider the effect of the offset in time between Thimerosal dosing and the diagnosis of autism or other autism spectrum disorder (ASD; the authors' pervasive developmental disorder [PDD]).

Finally, the medical records of these PDD-diagnosed children and their mother's were *not* evaluated to ascertain the estimated total nominal dose of Thimerosal that each PDD-diagnosed child *actually* received from conception to the date of the study's examination of the data.

"Measles-mumps-rubella coverage for each birth cohort was estimated through surveys of vaccination rates. The immunization schedule included a measles-mumps-rubella single dose at 12 months of age up to 1995, and a second measles-mumps-rubella dose at 18 months of age was added on after 1996."

This reviewer notes that relying on estimates from "*surveys of vaccination rates*" is particularly problematic when a second dose of a vaccine is added to a schedule during the period being assessed without the immunization data for the children being studied.

This is the case because a child born in the 1990s may have received one dose and been counted as immunized up until 1996.

However, *after 1996 begins*, a child may be subsequently classified as being out of compliance with the guideline because he or she did *not* get the recommended second dose of the measles-mumps-rubella (MMR) vaccine even when the first dose had been given.

**"RESULTS.** We found 180 children (82.8% males) with a pervasive developmental disorder diagnosis who attended the surveyed schools, yielding a prevalence for pervasive developmental disorder of 64.9 per 10000. The prevalence for specific pervasive developmental disorder subtypes were, for autistic disorder: 21.6 of 10000; for pervasive developmental disorder not otherwise specified: 32.8 of 10,000; and for Asperger syndrome: 10.1 of 10,000. A statistically significant linear increase in pervasive developmental disorder prevalence was noted during the study period."

First, the authors' reported "*pervasive developmental disorder of 64.9 per 10000*" translates into a 1 in 154 incidence rate.

Based on "180 (181/191)" total PDD cases reported, this incidence rate implies, *for 180 cases*, a population of about 27,718 to 27,756 children [with an average of about 27,737 children] (or, for 181 cases, 27,868 to 27,906 [with an average of about 27,889 children]).

Since the only reported "*registered*" population value was "*27749*," the reported incidence: **a)** seems reasonable and **b)** indicates that the included population size was, for this data, about the same as the reported "*registered*" value provided the included PDD total is "*180*" cases. [**Note:** Since the true PDD cases total was at least 190 (because the authors admit excluding 10 cases, the raw incidence rate for the population of "*registered*" students is 68.5 PDD cases per 10,000 registered students. In addition, this data would indicate that, on average, the class size should be about 2312 "*registered*" students in each grade)]

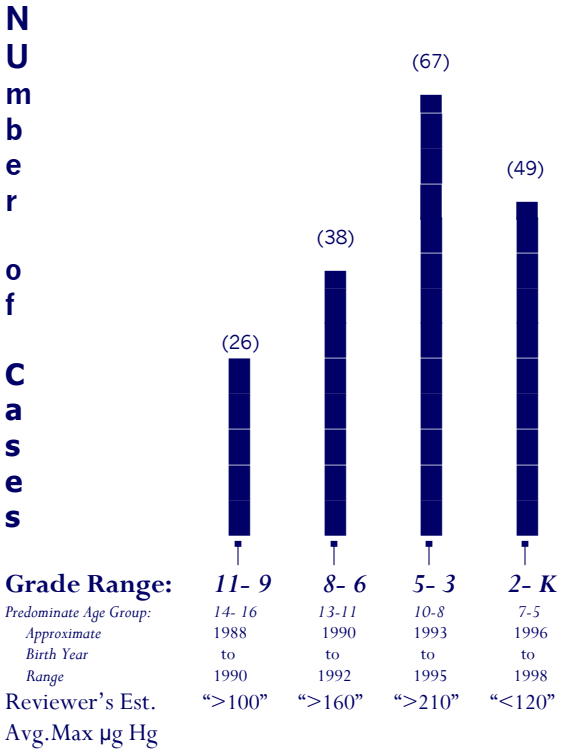
The "*prevalence*" for specific pervasive developmental disorder subtypes was reported as, *for autistic disorder with a reported 61 cases*, "*21.6 of 10000*" (**see** authors' "***Table 1***") or 1 "*autistic disorder*" case in every 463 registered students, which:

**a.** Is consistent with a registered school-district population of between about 28,176 and 28,306 (28,241, on average) for the 61 "*autistic disorder*" cases reported in three places in this study [**note:** this number is higher by, *on average*, 492 students than the "*27749*" value reported by the authors ("*As of October 1, 2003, a total of 27749 children were registered within the LBPSB*")],

**b.** Indicates that the incidence number reported by the authors here may have been be incorrect (since "*61*" cases and a population of "*27749*" gives an incidence rate of about 1 in 454.9 or about 21.98 per 10,000 [indicating: **i)** the reported incidence should have been 21.98 or 22.0 per 10,000 children, **ii)** the "*registered*" population number reported is *not* the number of children considered in the study], or **iii)** the number of "*autistic disorder*" cases is *not* "*61*" [**note:** in 3 of the 4 instances when the number of "*autistic disorder*" cases is mentioned, the authors report "*61*" cases – however, in the authors' "***RESULTS Prevalence***" section, they state (underlining added for emphasis): "*Of the remaining 89 children (49.4%), 60 children (33.3%) had a diagnosis of autistic disorder, 28 children (15.6%) had a diagnosis of Asperger syndrome, and 1 child (0.6%) had CDD*" – which does translate into a "*21.6 per 10,000*" incidence rate – this "cases" discrepancy again points to the need for all the data to be published], and, *in any case*,

**c.** Translates into a rate that less than 40% of the most recently US-reported incidence rate for "autism" of about 1 in 174 (about 55–59 "autism" ["*autistic disorder*"] cases per 10,000) for children "4 to 17" (**see:** Schieve LA, Rice C, Boyle C, Visser SN, Blumberg SJ. Mental health in the United States: Parental report of diagnosed autism in children aged 4--17 Years --- United States, 2003—2004. ***MMWR***. May 5, 2006; **55**(17): 481-486).

## Reviewer's Crude Bar Graph




Therefore, the Canadian "*autistic disorder*" rate reported here for children "*5 to 16*" is less than half of the *overall* U.S. survey rate (for the total included autism cases reported [567] relative to the total included number of acceptable survey documents returned

[98,475]) of about "1 in 174" children for "autism" in U.S. children "4 to 17" years of age.

Visual inspection of the authors' reported number of students by "age group" (**see** authors' "***Table 1***") indicates that there does *not* appear to be a linear increase in autism in this population provided the number of children in each grade are roughly equal (as shown in the "**Reviewer's Crude Bar Graph**").

Moreover, *if anything*, the actual drop in PPD incidence rates should be even more pronounced than the crude graph indicates because, *in general*, population growth (including immigration) *generally* favors an increase in the number of children (and hence PDD cases) in a given grade as the grade declines, provided the grade registration ascertainment numbers are all nearly 100% of the grade-eligible students in the school system studied.

Based on the preceding realities, this reviewer would, at a minimum, encourage the authors to publish the actual numbers of:

**a.** students and

**b.** cases of PDDs

in each grade so that the reported incidence numbers for at least the PDD cases could be verified.

Moreover, given the discrepancy found in the reported incidence rate of 21.6 per 10000 for the 61 autistic disorder cases in this reported 27,749 population of "*registered*" students and the approximate incidence rate computed by this reviewer (21.98 [or 22.0 per 10,000]), this reviewer suggests the authors need to double check all of their reported cases and incidence values.

Hopefully, the authors will, *in light of the preceding*, publish a complete table showing all of the individual data for each diagnosis and the actual class size used for each and every grade.

"The prevalence of pervasive developmental disorder in thimerosal-free birth cohorts was significantly higher than that in thimerosal-exposed cohorts (82.7 of 10000 vs. 59.5 of 10000)."

First, *as previously discussed*, there were no truly Thimerosal-free cohorts in the 1987–1998 period.

Second, the observed "relative numbers" do *not* appear to support either:

a. A "linear increase" in PPD, or

b. Higher incidence rates in the reduced-Thimerosal cohort (those in K through 2nd grade).

Moreover, the researcher's model failed to address the offset between Thimerosal exposure and the diagnosis of a given neurodevelopmental disorder.

Thus, the reported cohort rates seem to be at odds with the reality that the overall PPD cases were lower in the actual students in grades K through 2 ("*49*") than the number of PPD cases in actual students in grades 3 through 5 ("*67*") – values that seem to be at odds with the PPD incidence values reported in both of the article's figures.

Presuming that the numbers of students in each grade are approximately equal, then the "apparent average relative PPD for the actual student cases found would seem to be (after setting the relative cases to "1" for the for PPD cases in grade "9 – 11"-group): "1" for the 26

cases in the grade "9 – 11"-group; 38/26 ≅ 1.46 in the grade "6 – 8"-year-old group; 67/26 ≅ 2.58 in the grade "4 – 6" group; and "49/26" ≅ 1.88 in the grade "K – 2" group.

Based on this analysis, it would seem that the overall PPD cases found for the students having a PPD diagnosis did, *in fact*, decline by about "27%" in the "grade K – 2" group as compared to the cases of PDDs in the "grade 3 – 5" group – a decline in precisely those students who would, *on average*, have gotten a lower level of Thimerosal exposure than those in the "grade 3 – 5" group.

"Using logistic regression models of the prevalence data, we found no significant effect of thimerosal exposure used either as a continuous or a categorical variable. Thus, thimerosal exposure was unrelated to the increasing trend in pervasive developmental disorder prevalence."

Unless the actual numbers of students in each grade is significantly skewed, *which does not seem reasonable*, simple inspection of the numbers of *identified* students in each grade group clearly does *not* support the researchers "linear increase model" but they do support a drop in incidence after the average level of Thimerosal was significantly reduced in "1996."

Since the authors' fundamental assumptions seem to have been logically invalidated, the conclusions reached seemingly must similarly be questioned, if *not* rejected outright.

"These results were robust when additional analyses were performed to address possible limitations because of the ecological nature of the data and to evaluate potential effects of misclassification on exposure or diagnosis. Measles-mumps-rubella vaccination coverage averaged 93% during the study interval with a statistically significant decreasing trend from 96.1% in the older birth cohorts (1988–89) to 92.4% in younger birth cohorts (1996–1998). Thus, pervasive developmental disorder rates significantly increased when measles-mumps-rubella vaccination uptake rates significantly decreased. In addition, pervasive developmental disorder prevalence increased at the same rate before and after the introduction in 1996 of the second measles-mumps-rubella dose, suggesting no increased risk of pervasive developmental disorder associated with a 2–measles-mumps-rubella dosing schedule before age 2 years. Results held true when additional analyses were performed to test for the potential effects of misclassification on exposure or diagnostic status. Thus, no relationship was found between pervasive developmental disorder rates and 1- or 2-dose measles-mumps-rubella immunization schedule."

Since epidemiological absence of evidence of a connection *cannot* be used to establish evidence of the absence of a connection, the authors' *"no relationship was found between pervasive developmental disorder rates and 1- or 2-dose measles-mumps-rubella immunization schedule"* does *not* establish that no relationship exists.

Moreover, the important relationship that needed to be addressed, but that was *not*, is the relationship between: **a)** each case of pervasive disorder found including its category, date of onset, and direction of progression, and **b)** that case's vaccination history with respect to the MMR vaccine including vaccination date(s), vaccine lot(s) administered, other vaccines given, case's weight and general health on each vaccination date, and the adverse reactions to the MMR and other vaccines, if any.

Further, the concomitant drop in the level of Thimerosal in 1996 at the same "time" the MMR was being increased from 1 dose to 2 doses may be a significant confounding factor.

Finally, only those children born close to the time that the dosing change was made (in 1994 and after) are highly likely to have received the second MMR dose at or near the recommended 18-month time – if at all.

Thus, an effect attributable to an increase in the doses of MMR may have been obscured by a larger effect from the dropping of the maximum Thimerosal exposure level by 2 years of age from "> 210" µg to "< 120" µg in 1996 with the introduction of the "preservative free" pentavalent vaccine

"**CONCLUSIONS.** The prevalence of pervasive developmental disorder in Montreal was high, increasing in recent birth cohorts as found in most countries. Factors accounting for the increase include a broadening of diagnostic concepts and criteria, increased awareness and, therefore, better identification of children with pervasive developmental disorders in communities and epidemiologic surveys, and improved access to services."

First and foremost, no valid "*prevalence*" estimates were, or could be, established for "*Montreal*."

The nature (a English-speaking minority in Montreal – a predominately French-speaking city in a predominately French province, Quebec) and size (only 27,749 students across 12 school grades) of the population studied limits the findings to the apparent ***incidence*** of "*pervasive developmental disorder in*" the school system studied

The claims of: **a)** "*a broadening of diagnostic concepts and criteria*," **b)** "*increased awareness*" and **c)** increased "*identification of children with pervasive developmental disorders in communities and epidemiologic surveys*" have, *as far as this reviewer can ascertain*, only been asserted – no hard evidence has been provided for these effects in the children studied.

More importantly, in some countries, *like the United States and Denmark*, the authors' "*diagnostic concepts and criteria*," "*increased awareness*," and increased "*identification*" explanations have been found, *whenever scientifically assessed*, *not* to be valid for the period from the mid 1980s to date.

In fact, *in the United States' tracking of autism by the State of California*, the facts clearly indicate that the criteria for <u>including</u> a diagnosed, confirmed DSM "autism" case in the California autism disability database have been, *if anything*, slightly tightened (by effectively less than 1%) by adding inclusion criteria designed to reduce included cases because the State of California is, *by law*, required to provide monetary support for all included cases (**see** reviewer's **Appendix A**, **Ref. E-27**).

"The findings ruled out an association between pervasive developmental disorder and either high levels of ethylmercury exposure comparable with those experienced in the United States in the 1990s or 1- or 2-dose measles-mumps-rubella vaccinations."

Based on this reviewer's assessment of the little actual PDD data provided in this paper (**see** "**Reviewer's Crude Bar Graph**"), the study's PDD number findings have *not* "*ruled out an association between pervasive developmental disorder" (PDD) and "high levels of ethylmercury exposure*."

In fact, the reported "*PPD cases by*" *grade-group* data seems to indicate that there was a significant drop in PPD cases in/after 1996.

This is the case even though the data on mercury level was clearly biased by the failure to include either the mercury from the Thimerosal-preserved hepatitis B vaccine that, *in Quebec*, was reportedly given to more than 25% of the children in the 1996-1998 age group (mostly the students in *Grade K* through-*Grade 2*) or the mercury from the Thimerosal-preserved influenza vaccine that was also given to some children and/or their pregnant mothers who were high-risk-group members in the 1990s.

In instances, *as the case here*, where the exposure levels are variable and there is no data to account for significant sources of exposure (from the Thimerosal-preserved hepatitis B and influenza vaccines in this case), then the results (*of general epidemiological studies or reported case incidence rates studies that do not thoroughly investigate the actual vaccination history of each case of PDD cases but only look at the apparent levels of exposure for the "recommended" vaccines in the population*) *cannot* be used to disprove a linkage of the PPD case rates to the total Thimerosal exposure.

This is the case because the actual total Thimerosal exposures for the PDD cases and the non-PDD cases (controls) were *neither* accurately assessed *nor* addressed in the "studies" conducted by these authors.

Based on the reported overall PDD case data by grade groups, it would seem that there is some linkage between the "general" Thimerosal exposure levels and the PPD incidence rates by grade group.

Furthermore, this reviewer hopes that these authors will, *at a minimum*, fully disclose the numbers of the PDD cases and students in each grade, including any added from the special schools' list, so that the actual incidence rates for PDDs in the schools in question can be verified and the trends, *if any*, in those incidence rates more accurately evaluated.

Finally, since:

**a.** there was no marked change in the vaccination rate for the MMR vaccine over this period, and

**b.** the actual MMR vaccination status of the students with the PDDs was *not* assessed,

the association, *if any*, between MMR and PPD incidence *cannot* be reliably estimated – notwithstanding the assertions made by these authors.

"

---

**Key Words:** school-aged child • autism • Asperger syndrome • childhood disintegrative disorder • pervasive developmental disorder • prevalence • epidemiology • immunization • thimerosal • ethylmercury • measles vaccine • MMR

**Abbreviations:** PDD—pervasive developmental disorder • PDDNOS—pervasive developmental disorder not otherwise specified • CDD—childhood disintegrative disorder • MMR—measles-mumps-rubella • LBPSB—Lester B. Pearson School Board • MEQ—Ministry of Education of Quebec • DSM-IV—Diagnostic and Statistical Manual of Mental Disorders—Fourth Edition • Hib—Haemophilus influenzae type b • CI—confidence interval • OR—odds ratio • df—degrees of freedom

Pervasive developmental disorders (PDDs) are characterized by marked impairments in reciprocal social interaction, language, and communication and by the presence of repetitive/stereotypic patterns of behavior and interests.[1] PDDs refer to a class of disorders that is composed of several diagnoses, including autistic disorder, PDD not otherwise specified (PDDNOS), Asperger syndrome, and childhood disintegrative disorder (CDD). Rett disorder has been historically listed in the PDDs to

enhance differential diagnosis, but it is usually not included in studies of children with PDD. Investigations of the causes of PDDs are progressing, especially with respect to molecular genetic studies.[2] Early intensive behavioral interventions can significantly alter developmental trajectories of preschoolers and may lead to substantial cognitive and language gains in some children.[3,4] Yet, some children make little gains,[4] and the long-term outcome of PDDs, and particularly that of autistic disorder, is still guarded.[5] Services for children with PDDs are in great need of development in many countries, including Canada.

Epidemiologic surveys of PDDs have multiplied in recent years. Reviews[6,7] and surveys[8,9] conducted in the last 5 years have consistently reported prevalence rates of 0.6% for the whole PDD spectrum."

This reviewer only notes that this "*0.6% for the whole spectrum*" is, *coincidently*, also the same as the 1 in 166 figure for autistic spectrum disorders (ASDs) in the 2004 "**Autism A.L.E.R.T.**" jointly issued by the United States Department of Health and Human Services (DHHS), Centers for Disease Control and Prevention (CDC), Food and Drug Administration (FDA), and the American Academy of Pediatrics (AAP).

"This roughly threefold increase in PDD prevalence over time[10] has generated concerns about a possible epidemic, although a true secular increase in the incidence of the disorder has not yet been demonstrated.[7,11,12] Rather, factors such as broadening of the diagnostic concepts, increased awareness of the disorder, and improved detection in surveys likely account for a substantial part of the increased prevalence.[7,12–15],,

In general, *as discussed in the review of the authors' abstract*, the declarations made in the authors' references have been made without scientifically sound and appropriate proof that clearly established the validity of the assertions made by the authors in the references cited.

Moreover, these issues were explicitly considered and refuted in the report assessing the autism-case incidence in California that was published by the M.I.N.D. institute in 2002 (**see** reviewer's **Appendix A**, **Ref. E-27**).

SINCE:

- These "incidence increase confounding" factors have been unequivocally shown *not* to be factors for autism and
- There has not been any significant increase in the re-diagnosis of people in their 30s, 40s, and 50s with a PDD diagnosis as would be required to logically support the authors' assertions,

THEN, this reviewer, and others who also rely on science-based findings and *not* unsupported assertions based on little or no scientifically sound supporting data or logical substance, must conclude:

- The observed PDD case increases (and decreases) seen in a small sample of "*Canadian*" children studied by the authors of this paper are real and
- The mercury from Thimerosal is a major factor in the ***increases*** (*and* ***decreases***) in the incidence rates for the PDDs found in this study of a small sample of "*Canadian*" children as well as those incidence increases found by the CDC researchers in their *initial* studies ("Phase 0" and "Phase 1") on managed-care-organization records for California children that were entered, and supposedly continue to reside, in the Vaccine Safety Datalink (VSD) database. [**Note:** The Geiers have consistently found epidemiological evidence of a linkage between the differences in

Thimerosal exposure and differences in the rates of neurodevelopmental disorders (in all of the databases, *including the VSD*, which they have examined using the same valid epidemiological tools and study designs that the CDC has long recognized as being valid and has itself used for the various databases studied).]

"If changes in the incidence of PDDs were demonstrated, they might point toward environmental risk factors contributing to the etiology of the disorder, with or without gene interactions."

This reviewer agrees with the authors here.

In addition, this reviewer notes, *to this reviewer's satisfaction*, both the ***increases*** and ***decreases*** in annual PDD cases track, *with an appropriate offset*, the changes in the maximum levels in mercury from Thimerosal-preserved vaccine shots in the period being studied by these authors provided, *for reasons that are readily apparent to this reviewer and, in the Grade 11 case, were apparent to the authors*, the uncorrected incidence data from *Grade 11* and *Grade K* are excluded from this study (as they should have been). [**Note:** Instead of omitting the anomalous uncorrected data point for *Grade 11*, the authors of this paper "corrected" it. In the case of the anomalous *Grade K* data point, the authors seemingly ignored the problems associated with it and, *based on the manner in which they reported the data*, attempted to conceal the apparent class-size denominator anomaly in the PPD incidence for Grade K.]

"Few environmental exposures that occur during the prenatal period have been related to increased risk of PDDs, and such factors account for only a tiny fraction of the population risk.[16] However, hypotheses linking vaccinations to autism have been raised since 1998. The first hypothesis implicated the measles component of the measles-mumps-rubella (MMR) vaccine that is usually given to children between 12 and 15 months of age in most countries.[17],"

Wakefield *et al*. did *not* hypothesize that the MMR vaccine was *causatively* linked to autism or PDDs in general.

Those researchers *only* noted a statistically significant increase in the abnormal incorporation of parts of the measles virus' genetic material in "PPD children" diagnosed with gastrointestinal dysfunction as compared to "non-PPD children" having gastrointestinal problems.

"Subsequent epidemiologic investigations of this hypothesis have consistently failed to establish an association between MMR and autism in cohort,[18] case-control,[19,20] and ecological studies.[21–23] Furthermore, clinical studies have also failed to identify a clinical phenotype characterizing a smaller group of autistic children presumably at risk of MMR-induced autism.[24] Recent reviews of the MMR hypothesis by an *ad hoc* committee of the Institute of Medicine and the Cochrane collaboration concluded that the evidence favored the rejection of this hypothesis.[25,26] Yet, concerns about MMR safety have persisted among parents of autistic children and the lay public, leading to decreased uptake of the vaccine and subsequent measles epidemic outbreaks.[27] In addition, no study has ever tested the effects of a 2-MMR dosing schedule in toddlers.

A second hypothesis implicated the cumulative exposure of young children until age 2 years to thimerosal, a vaccine stabilizer that contains 50% ethylmercury. This hypothesis is entirely distinct from the previous one, because MMR vaccines never contained any thimerosal because it would inactivate a live vaccine."

In this reviewer's view, the researchers have misstated the general "Thimerosal hypothesis" here.

The general "Thimerosal hypothesis" holds:

> The injection of Thimerosal-preserved biological drugs, *indirectly into the fetus by injecting the mother and, after birth, directly into the neonate, baby, toddler, child, adolescent, adult and elderly person*, mercury poisons all those so treated to the point that some, *after some level of exposure*, exhibit all of the clinical symptoms of mercury poisoning that are used to diagnose "autism" in children as well as the clinical symptoms for other effects from the sub-acute mercury poisoning of children by injecting their mothers, during pregnancy, or the children or others, at some times after their birth, with, typically, 25- to 50-microgram doses of Thimerosal (12.5- to 25- microgram doses of mercury) from the Thimerosal-preserved vaccines and other Thimerosal-preserved biological products with which they are directly or indirectly exposed by vaccination.

Further, this reviewer also notes that if 0.01% Thimerosal is toxic to disease viruses, it should be obvious that Thimerosal is also toxic to human cells at that level.

Moreover, actual studies have long shown that Thimerosal is up to "35" times more toxic to human cells and tissues than it is to pathogenic bacteria (**see Appendix A, Ref. C-116**).

"A review of the US immunization schedule concluded that the cumulative exposure of children at age 2 years exceeded US Food and Drug Administration and US Environmental Protection Agency recommended safety limits and led to the suggestion in the United States to remove thimerosal from vaccine preparations altogether.[28,29] Subsequent epidemiological research on the thimerosal-autism presumed association has been consistently negative, with cohort[30–33] and ecological[34,35] studies failing to show any association."

The researchers fail to note the initial findings of the CDC's Verstraeten group (published at: http://www.safeminds.org/research/library/GenerationZeroNotes.pdf), which clearly show a strong positive correlation between the maximum level of post-partum Thimerosal exposure and the incidence of autism.

In addition, the researchers fail to note that even the multiply iterated and intentionally biased published CDC Verstraeten-group study found positive correlations between Thimerosal exposure level and the incidence of some neurodevelopmental disorders.

These outcomes were observed for some vaccination time points in spite of that group's inappropriately assigning up to a < 37.5-microgram of mercury exposure (<75 micrograms of Thimerosal) to the "zero" group and truncating the maximum exposure at the ≥ 62.5-microgram level — and essentially excluding those children with levels of exposure greater than 150 micrograms (µg) of mercury (> 300 µg of Thimerosal) by 2 years of age.

Moreover, *to obscure the risks observed*, the values they reported were *not* stated in terms of an odds ratio (OR) but rather as the relative risks (RR) "**by increase per 12.5 µg of Hg exposure from TCVs**" (**see**, for example, **Tables 3** and **4** in the published 2003 ***Pediatrics*** paper by Verstraeten *et al*. [**ref:** Verstraeten *et al*. Safety of Thimerosal-containing vaccines: A two-phased study of computerized health maintenance organization databases. ***Pediatrics***. November 2003; **112**(5): 1039–1048]; this reviewer's **Ref. E-18**]).

For the reader's convenience, the **Tables 3** and **4** that this reviewer is referencing from the published study cited have been recreated on this page (with **bolding** added to the

reported "**RR**" and "**95% CI**" values for the relative rates that are probably greater than 1.00).

"The only published 'positive' studies have all been performed by 1 author[36,37] and have been considered to be noncontributing because of their poor methodology.[25,38],,

This reviewer notes that the authors' statement here is factually incorrect, because the Internet-published Phase "0" and Phase "1" results found by the CDC's "Verstraeten group" are most clearly "*published 'positive' studies*" (**references:** For the Phase "0" results, http://www.safeminds.org/research/library/GenerationZeroNotes.pdf and, for the Phase "1," the findings reported in SafeMinds' critique of the published VSD study results at: http://www.safeminds.org/research/library/VSD_SafeMinds_critique.pdf.

"**TABLE 3. RRs by Increase of 12.5 µg of Hg Exposure From TCVs at HMO A**

| | 1-Month Cumulative Hg | | 3-Month Cumulative Hg | | 7-Month Cumulative Hg | |
|---|---|---|---|---|---|---|
| **Outcome** | **RR** | **95% CI** | **RR** | **95% CI** | **RR** | **95% CI** |
| **Stammering** | 0.89 | 0.40–1.97 | **1.18** | **0.74–1.89** | **1.17** | **0.97–1.41** |
| **Tics** | **1.25** | **0.47–3.29** | **1.89*** | **1.05–3.38** | **1.12** | **0.93–1.34** |
| **Sleep disorders** | 0.79 | 0.38–1.61 | 0.93 | 0.71–1.21 | **1.08** | **0.95–1.24** |
| **Emotional disturbances** | 1.00 | 0.42–2.36 | 0.98 | 0.66–1.45 | 0.92 | 0.81–1.03 |
| **ADD** | 0.92 | 0.52–1.59 | 0.83 | 0.68–1.02 | 0.93 | 0.84–1.02 |
| **Speech delay** | **1.07** | **0.83–1.38** | **1.03** | **0.93–1.15** | 0.97 | 0.92–1.01 |
| **Speech/language delay** | **1.14** | **0.88–1.46** | **1.03** | **0.93–1.14** | 0.97 | 0.93–1.02 |
| **Coordination Disorders** | **1.67** | **0.78–3.57** | **1.19** | **0.82–1.71** | 1.00 | 0.87–1.15 |

**CI indicates confidence interval.**

*** P < .05.**

"

and

"**TABLE 4. RRs by Increase of 12.5 µg of Hg Exposure From TCVs at HMO B**

| | 1-Month Cumulative Hg | | 3-Month Cumulative Hg | | 7-Month Cumulative Hg | |
|---|---|---|---|---|---|---|
| **Outcome** | **RR** | **95% CI** | **RR** | **95% CI** | **RR** | **95% CI** |
| **Autism** | **1.16** | **0.78–1.71** | **1.06** | **0.88–1.28** | 1.00 | 0.90–1.09 |
| **Other child psychosis** | **1.03** | **0.60–1.74** | 0.93 | 0.73–1.19 | **1.04** | **0.91–1.20** |
| **Stammering** | 0.61 | 0.33–1.14 | **1.10** | **0.86–1.41** | **1.06** | **0.93–1.21** |
| **Tics** | 0.85 | 0.55–1.30 | 0.95 | 0.78–1.15 | **1.09** | **0.98–1.21** |
| **Sleep disorders** | **1.24** | **0.80–1.93** | **1.15** | **0.95–1.39** | **1.09** | **0.99–1.19** |
| **Eating disorders** | 0.90 | 0.50–1.61 | 0.97 | 0.72–1.29 | 0.98 | 0.85–1.14 |
| **Emotional disturbances** | 0.76 | 0.54–1.07 | **1.02** | **0.88–1.18** | **1.01** | **0.93–1.10** |
| **ADD** | 0.90 | 0.74–1.10 | **1.01** | **0.93–1.11** | **1.02** | **0.97–1.07** |
| **Language delay** | **1.06** | **0.83–1.35** | **1.13*** | **1.01–1.27** | **1.07*** | **1.01–1.13** |
| **Speech delay** | **1.02** | **0.90–1.17** | **1.04** | **0.98–1.10** | **1.02** | **0.99–1.05** |
| **Language/speech delay** | **1.03** | **0.91–1.17** | **1.05** | **0.99–1.11** | **1.02** | **0.99–1.05** |

*** P < .05.**

"

Furthermore, *other than statements in the authors' references "25" and "38" that the referenced studies used "poor methodology,"* the authors in those articles presented little, or no, factual information to support their assertions.

In addition, other anonymous critics have falsely asserted that the Geiers did *not* have access to the dose distribution figures (the "denominators") that they used when the critics knew, or should have known, that the Geiers actually did have that information but did *not* publish

those data because the Geiers had agreed to hold it in confidence in exchange for that denominators information's being provided to them by the government.

Furthermore, authors of this paper failed to note the other positive epidemiological papers published in 2003, 2004, and 2005 (before this article was accepted for publication in 2006 ["*Accepted Feb 15, 2006*"]) in various recognized peer-reviewed journals by the "*1 author*" (actually, 2 collaborative authors) to which they allude, including the following articles:

1. Geier MR, Geier DA. Neurodevelopmental disorders after thimerosal-containing vaccines: a brief communication. ***Exp Biol Med (Maywood)***. 2003 Jun; **228**(6): 660-664.
2. Geier DA, Geier MR. An assessment of the impact of thimerosal on childhood neurodevelopmental disorders. ***Pediatr Rehabil***. 2003 Apr-Jun; **6**(2): 97-102.
3. Geier DA, Geier MR. A comparative evaluation of the effects of MMR immunization and mercury doses from thimerosal-containing childhood vaccines on the population prevalence of autism. ***Med Sci Monit***. 2004 Mar; **10**(3): PI33-139.
4. Geier DA, Geier MR. An evaluation of serious neurological disorders following immunization: a comparison of whole-cell pertussis and acellular pertussis vaccines. ***Brain Dev***. 2004 Aug; **26**(5): 296-300.
5. Geier DA, Geier MR. Neurodevelopmental disorders following thimerosal-containing childhood immunizations: a follow-up analysis. ***Int J Toxicol***. 2004 Nov-Dec; **23**(6): 369-376.
6. Geier DA, Geier MR. A two-phased population epidemiological study of the safety of thimerosal-containing vaccines: a follow-up analysis. ***Med Sci Monit***. 2005 Apr; **11**(4): CR160-CR170.

This reviewer notes that, *as far as he can ascertain*, no critiques of the epidemiological methodology used in any of these six (6) additional papers have been published in any peer-reviewed journal.

In addition, the Geiers' study in the Vaccine Safety Datalink (VSD) database using the CDC-recommended epidemiological-study approaches in their **reference-6** paper confirmed and supported their earlier findings including those questioned in this article's references "*36*" and "*37*."

"By and large, biological studies of ethylmercury exposure have also failed to support the thimerosal hypothesis.[25,39,40],,

This reviewer notes that the authors have failed to report the hundreds of studies that delineate the systemic toxicity, including neurological damage, and other adverse effects caused by mercury, inorganic mercury salts and organic mercury compounds, including Thimerosal.

Collectively, these studies overwhelmingly support the validity of the Thimerosal "*hypothesis*" that these authors are seeking to discredit in this paper.

## Table R-1: List of U.S.-licensed Thimerosal-preserved Human Biological Products Currently In Distribution in the United States,[1] As of October 4, 1999

| Vaccine | Registered Trade Name | Licensed Manufacter[2] | Thimerosal Concentration. In µg per mL | Thimerosal in µg/dose Adult (child [if less]) |
|---|---|---|---|---|
| Allergen Extracts[3] | Various | Various | 100 | Variable (variable) |
| Allergen Patch Test | T.R.U.E. Test | Pharmacia Res. Cntr | 6.5 µg per patch | |
| Coccidioidin | Spherilin | ALK Labs | 100 | Not reported |
| DTaP adsorbed | Certiva | North American Vaccine | 100 | 50 µg/0.5 mL |
| | ACEL-IMUNE | Lederle | 100 | 50 µg/0.5 mL |
| | Tripedia | CLI | 100 | 50 µg/0.5 mL |
| DTP adsorbed[4] | Tri-Immunol | Lederle | 100 | 50 µg/0.5 mL |
| DTP adsorbed | --- | CLI | 100 | 50 µg/0.5 mL |
| | --- | Wyeth | 100 | 50 µg/0.5 mL |
| | --- | Bioport | 100 | 50 µg/0.5 mL |
| DTP adsorbed[4] | --- | MPHL | 100 | 50 µg/0.5 mL |
| DT adsorbed | --- | CLI | 100 | 50 µg/0.5 mL |
| | --- | MPHL | 100 | 50 µg/0.5 mL |
| | --- | Bioport | 100 | 50 µg/0.5 mL |
| | --- | Wyeth | 100 | 50 µg/0.5 mL |
| D[4] | --- | CLI | 100 | 50 µg/0.5 mL |
| D adsorbed[4] | --- | Bioport | 100 | 50 µg/0.5 mL |
| Td adsorbed | --- | Lederle | 100 | 50 µg/0.5 mL |
| | --- | CLI | 100 | 50 µg/0.5 mL |
| | --- | MPHL | 33 | 16.5 µg/0.5 mL (8.25 µg /0.25mL) |
| | --- | Wyeth | 100 | 50 µg/0.5 mL |
| TT fluid | --- | CLI | 100 | 50 µg/0.5 mL |
| | --- | Wyeth | 100 | 50 µg/0.5 mL |
| TT adsorbed | --- | CLI | 100 | 50 µg/0.5 mL |
| | --- | Lederle | 100 | 50 µg/0.5 mL |
| | --- | Bioport | 100 | 50 µg/0.5 mL |
| | --- | MPHL | 100 | 50 µg/0.5 mL |
| | --- | SSVI | 100 | 50 µg/0.5 mL |
| | --- | Wyeth | 100 | 50 µg/0.5 mL |
| P[4] | --- | Bioport | 100 | 50 µg/0.5 mL |
| DTP-HIB | TETRAMUNE | Lederle | 100 | 50 µg/0.5 mL |
| | ActHIB + DTP | PM | 100 | 50 µg/0.5 mL |
| HIB[5] | HIBtiter (multidose only) | Lederle | 100 | 50 µg/0.5 mL |
| HIB[6,7] | PedvaxHIB (lyophilized only) | Merck | 50 | 25 µg/0.5 mL |
| HIB | ProHIBit | CLI | 100 | 50 µg/0.5 mL |
| Hepatitis B | Energix B | SKB | 50 | 50 µg/1.0 mL (25 µg/0.5 mL) |
| | Recombivax B | Merck | 50 | 50 µg/1.0 mL (25 µg/0.5 mL) |
| Influenza | Fluviron | Medeva | 100 | 50 µg/0.5 mL (25 µg/0.25 mL) |

[1] NIEH NIH Report: *Thimerosal [54-64-8]: Nomination to the national toxicology program. Review of the literature*. April 2001, pp. 28–33

[2] Manufacturers Abbreviations: CLI (Connaught Laboratories, Inc. – Pasteur Merieux Connaught USA), CLL (Connaught Laboratories, LTD), MBPI (Michigan Biologic Products Institute), MPHL (Massachusetts Public Health Biologic Laboratories), PM (Pasteur Merieux Serums et Vaccins, SA), SKB (SmithKlineBeecham Biologicals), SSVI (Swiss Serum and Vaccine Institute, Berne).

[3] Allergen extracts usually contain 0.4% or 0.5% phenol. Thimerosal may be if allergen darkens in the presence of phenol (extracts of privet pollen, mushroom, grain mill dist, white potato, avocado; food extracts of corn, barley, oat, rye, and wheat). Reference: ImmunoFacts 1999.

[4] Not currently distributed in the U.S.

[5] HIBtiter in single-dose vials does not contain Thimerosal

[6] Lyophilized PedvaxHIB no linger distributed in U.S. (personal communication Dr. Carlo Russo, Merck, 6/25/1999)

[7] Diluent contains Thimerosal, unreconstituted lyophilized product does not.

**Table R-1: List of U.S.-licensed Thimerosal-preserved Human Biological Products Currently In Distribution in the United States,[1] As of October 4, 1999** (Cont.)

| Vaccine | Registered Trade Name | Licensed Manufacter[2] | Thimerosal Concentration. In µg per mL | Thimerosal in µg/dose Adult (child [if less]) |
|---|---|---|---|---|
| **Influenza** (whole viron) | **Fluzone** | **CLI** | **100** | **50 µg/0.5 mL** |
| **Influenza (subviron)** | **Fluzone** | **CLI** | **100** | **50 µg/0.5 mL (25 µg/0.25 mL)** |
| **Influenza** | **FluShield** | **Wyeth** | **100** | **50 µg/0.5 mL (25 µg/0.25 mL)** |
| **Influenza** | **Fluogen** | **Parkdale** | **100** | **50 µg/0.5 mL** |
| **Japanese Encephalitis** | **JE-VAX** | **CLI (Biken)** | **70** | **70 µg/1.0 mL (35 µg/0.5 mL)** |
| Meningococcal A[4] | Meningococcal -A | CLI | 100 | 50 µg/0.5 mL |
| Meningococcal C[4] | Meningococcal-C | CLI | 100 | 50 µg/0.5 mL |
| Meningococcal A/C[4] | Meningococcal-A/C | CLI | 100 | 50 µg/0.5 mL |
| **Meningococcal A/C/W/Y-135 (lyophilized)[7]** | **Menimune A/ C/ W/Y-135** | **CLI** | **100** | **50 µg/0.5 mL** |
| **Mumps Skin Test Antigen** | **MSTA** | **CLI** | **100** | **10 µg/0.1 mL** |
| **Pneumociccal** | **Pnu-Imune 23** | **Lederle** | **100** | **50 µg/0.5 mL** |
| Rabies[4] | RABIE-VAX | CLL | 100 | 50 µg/0.5 mL |
| **Rabies** adsorbed | **---** | **Bioport** | **100** | **100 µg/1.0 mL** |
| **Immune Globulin** | **---** | **Bioport** | **100** | **variable** (by weight) |
| Immune Globulin[8] | --- | Centeon | 100 | **variable** (by weight) |
| Immune Globulin[8] | --- | Immuno-US | 100 | **variable** (by weight) |
| Hepatitis B Immune Globulin[8] | --- | Abbott | 100 | **variable** (by weight) |
| **Rho (D) Immune Globulin** | **MICRhoGAM RhoGAM** | **Ortho-Clinical Diagnostics** | **30-33** | **21-33/0.7-1.0mL** |
| **Vaccina Immune Globulin[9]** | **----** | **Baxter** | **100** | **variable** (by weight) |

[1] NIEH NIH Report: *Thimerosal [54-64-8]: Nomination to the national toxicology program. Review of the literature.* April 2001, pp. 28–33

[2] **Manufacturers Abbreviations: CLI (Connaught Laboratories, Inc. – Pasteur Merieux Connaught USA), CLL (Connaught Laboratories, LTD), MBPI (Michigan Biologic Products Institute), MPHL (Massachusetts Public Health Biologic Laboratories), PM (Pasteur Merieux Serums et Vaccins, SA), SKB (SmithKlineBeecham Biologicals), SSVI (Swiss Serum and Vaccine Institute, Berne).**

[7] **No longer in active production or distribution (Dr. Thomas Lynch, Office of Blood Research and Review, 7/21/1999).**

[8] **Produced for Department of Defense. Only one lot exists at one time, with a new lot made when the previous one becomes outdated.**

These references include, *but are not limited to*, the significant articles listed in this reviewer's **Appendix A** and the pertinent references in them that bear on the issues of toxicity, safety, adverse reactions, and compliance with the applicable statutes and laws as they apply to Thimerosal (49.55% mercury by weight) and other mercury species in all of their uses as well as a table (**see** reviewer's **Table R–1** on this and the preceding pages) of the status of US-licensed human vaccines and other human Thimerosal-preserved biological products in 1999:

"Despite the accumulation of negative studies, concerns from the public have not been entirely alleviated, and fears continue to be fueled by well-publicized media accounts of a spectacular nature.[41,42,,]

First, this reviewer finds that there is no "*accumulation of negative studies*" as the authors assert.

Second, this reviewer finds that the authors' two references, "*41. Kennedy RF Jr. Deadly immunity. Available at: www.rollingstone.com/politics/story. Accessed June 20, 2005*" and "*Kirby D. Evidence of Harm: Mercury in Vaccines and the Autism Epidemic—A Medical Controversy. New York, NY: St. Martin's Press; 2005*," are neither "*well-publized*" nor "*spectacular*" but rather:

**a.** *Compared to even this article*, little publicized by the mainstream media,

**b.** More matter of fact than "*spectacular*," and

**c.** With respect to the book, **Evidence of Harm**, this book's author presents a balanced account of what has transpired and his presentation is simply factual.

"Unfortunately, these unsubstantiated claims have led to the uncontrolled development of chelation therapies of autistic children in North America."

Here, the authors begin with an unsubstantiated "a led to b" premise, "*these unsubstantiated claims have led to the uncontrolled development of chelation therapies of autistic children in North America*" that ignores the reality that the nexus for the authors' "*uncontrolled development of chelation therapies of autistic children*" lies in:

**a.** The failure of the "mainstream medical establishment" to recognize that the symptoms they were observing were the same as those proven to be caused by subacute mercury poisoning, and

**b.** The refusal of that establishment to recognize the value of chelation in such cases even though that establishment has wholeheartedly embraced the chelation of children to remove lead from paint and leaded gasoline exposures and other sources – *apparently* because the paint and gasoline industries are at fault and ***not***, *as in the current mercury-poisoning situation*, the healthcare establishment and its practices, which have been shown to be, and are, major contributing factors to the mercury-poisoning harm observed.

"These therapies are not only of unproven efficacy, but they also can be dangerous, as unfortunately shown in the recent death of a 5-year-old boy with autism.[43]"

Contrary to the authors' views, the danger is *not* in the chelation per se.

Factually, the "*5-year-old boy*" in question died because of a medical error; the wrong form of EDTA, a sodium form, was used instead of the prescribed calcium EDTA drug.

Thus, all that this boy's death proved was "*dangerous*" was the doctor's failure to ensure the prescribed medication was administered – a medical error – *not* chelation *per se*.

In addition, *when the available intravenous chelation therapies are removed from use for heavy-metal detoxification*, the risk of death from a medical error from the use of the wrong form of EDTA is virtually eliminated.

This is the reality because these other approaches generally employ the long-used and recognized chemical chelating drugs (e.g., DMSA and DMPS) or dietary supplements (e.g., NAC [N-acetyl-cysteine], ALA [alpha-lipoic acid], and vitamin C [ascorbic acid]) and/or foods (e.g., algal products like chorella) in the form of solid dosage units

(tablets, capsules, and suppositories) and powders that are generally administered by a "knowledgeable" caring parent.

"Only 1 survey of autism spectrum disorders has thus far been performed in Canada.[44] The authors screened 20800 children aged 4 to 6 years residing in a specific region of Nova Scotia in 1985 and, using new research diagnostic criteria, obtained a prevalence of 10.1 per 10000 children for autism."

This reviewer only notes that the incidence of "*10.1 per 10000 children for autism*" matches the about "10" cases of autism per 10,000 children reported by Denmark during the period from 1982 to 1986 when, before the introduction of the MMR vaccine there in 1987, the only received a Thimerosal-preserved vaccine that Danish children received was the DPT shot series – similar to the national vaccination program for Thimerosal-preserved vaccines in Canada (**see:** Stott C, Blaxill M, Wakefield AJ. MMR and autism in perspective: The Denmark story. ***J Am Phys Surg***. 2004 Fall; **9**(3): 89-91, **Figure 2**, page 90).

"This survey did not generate a figure for the whole PDD spectrum, and dates back 20 years. No epidemiological survey has ever been conducted in Quebec or in other parts of Canada. As other provinces in Canada, Quebec has a universal health insurance system that ensures free access to medical care. As a result, immunization policies are effectively implemented at the population level. In the last 20 years, several changes in the official immunization schedule occurred that provided an opportunity to assess the effects, if any, of both variations in thimerosal exposure and MMR vaccine coverage on PDD rates in successive birth cohorts."

Factually, the "*several changes in the official immunization schedule*" as well as the authors' failure to include the Thimerosal-preserved hepatitis-B vaccine given to a substantial percentage of the children in Quebec and the Thimerosal-preserved inactivated influenza vaccine given to some children and pregnant women in "high risk" groups" in Quebec though neither of these Thimerosal-preserved vaccines are in "*in the official immunization schedule*" have actually made it much more difficult to accurately assess the exact magnitude of the effect of Thimerosal-preserved vaccines on the incidence rate and distribution of PDD cases during the interval where those changes were being made.

Moreover, *in contrast to the authors' portrayal of the changes as "instantaneous" events*, each Thimerosal-level change is *not* instantaneous but occurs over some period of time in some unspecified portion of this in the population during a "time window," *though not addressed in the article*, over which the actual change occurs.

Further complicating this picture is the fact that diagnosis of a PDD case is usually delayed by some months to years from the time for the initial point in any change window.

Moreover, the authors' refusal to find and use the ages of all the children in this school system rather than their grade further increases the assessment uncertainties in such relationship evaluation studies because, contrary to the authors' claims, the only valid epidemiological assessments the authors could have validly made from the data they report collection are grade evaluations – *not* the age-related evaluations that the authors claim to have made.

Based on the preceding realities, the "*variations in thimerosal exposure and MMR vaccine*" doses actually interfere with the "*opportunity to assess the effects, if any, of both variations in thimerosal exposure and MMR vaccine coverage on PDD rates in successive birth cohorts*."

Finally, because the authors have gathered grade cohort data and *not* birth cohort data, no scientifically valid assessments of the effects of changes in Thimerosal exposure or the change in the number of MMR vaccine doses can be made "*in successive birth cohorts*."

"We report here on a prevalence survey of PDDs that we conducted in 2003–2004 in a Montreal school board. The goals of this survey were to (1) generate an estimate of the prevalence of the whole PPD spectrum that could be applied to the province of Quebec for purposes of service planning, (2) estimate the prevalence of specific diagnostic subtypes within the PDD spectrum, (3) evaluate trends in prevalence rates in successive birth cohorts, (4) examine the relationship, if any, between trends in autism rates and exposure to varying levels of thimerosal during the study period, and (5) examine the relationship, if any, between trends in autism rates and MMR vaccination uptake. Compared with previous research on immunization and autism, this study uniquely examines exposure to high levels of thimerosal and also tests for the effects of a 2-dose MMR schedule before age 2 years."

With respect to the authors' goals, this reviewer finds that they did "*(1) generate an estimate of the*" incidence "*of the whole PPD spectrum*."

However, *because the estimates for each "putative age"/grade range or grade are not the same*, no single estimate can be provided.

In addition, *lacking the enrollment and total PDD cases data for each grade*, this reviewer *cannot* precisely assess the validity of the reported PDD incidence data for each grade.

However, beginning with the total number of students stated, the number of PPD cases in each grade range (9–11, 6–8, 3–5 and K–2), the authors' reported incidence rates for each grade (in, *for example*, the authors' "***Figure 1***"), and an initial presumption of about a similar number of students in each of the 12 grades (about 2150 – 2700 per grade) and iterating the data without constraining the total number enrolled, it becomes apparent that:

- ***For grades 3-11***, the numbers of students in each grade group is about as expected (about 2200 in average in grades 8–11, about 2400 in grades 6–8, and about 2600 in grades 3-5 or a total guesstimated enrollment of 21,600 leaving about 6150, for a total registration of "*27749*," less than the expected 7800-plus (given the trends seen) for grades K–2, but
- ***For grades K-2***, the guesstimated number in each grade that iterated to the total cases and individual "grade" incidences reported was "2545" for grade 2, "2734" for grade 1, but only about "1022" for grade K – a number that indicates that, *for some unmentioned reason*, the number of students in the *Grade K* group was significantly less that in any other grade groups.

Visually, the 107.6 incidence-rate value for the *Grade K* group also seems to be much higher than expected.

Unfortunately, the reported total number of students, "*27749*" is the only item in the iterative evaluation of the data that was different than the reported total (estimated total was "~ 28210–28,330" – an overall ~ 460 – 580 student excess. [**Note:** On 27 July 2006, this reviewer emailed Dr. Fombonne a request (**see Appendix B, Exhibit 1** for a copy of this initial request) for the needed enrollment and case data for each grade so that the reason for the differences found could be addressed. A call to his number on 4 August 2006 found that Dr. Fombonne was on vacation until 14 August 2005. Calls on 15 and 16 August reached an assistant who repeatedly said she would give Dr. Fombonne this reviewer's messages. On 18 August 2006, this reviewer sent him another email (**see Appendix B, Exhibit 2** for a copy of this email request) that set a cutoff date for a reply as the end of 21 August 2006 and indicated that a failure to respond by that date would indicate Dr. Fombonne's unwillingness to share the requested information with this reviewer. As of 21 August

2006, Dr. Fombonne has apparently elected *not* to provide the requested information *nor* responded to any of this reviewer's emails or telephone messages requesting the information required to verify the "incidence" rates reported in this article for which he is the contact author.]

*Even ignoring the enrollment difference found in the estimates*, the only way this reviewer found that the reported incidence rates can have been found for a group of "28,000" enrolled students is if the numbers of students in grade K is significantly less than 2000 students – indicating that *Grade K* attendance is optional resulting in: **a)** significantly less than the "*registration*" seen in the other grades and/or **b)** a disproportionately high relative number of the registered PPD cases in the schools' *Grade K* enrollment.

**Reviewer's Guesstimated Approximate "Grade" Data[1]**

| Grade | Estimated Students (S) | Estimated Total PPD Cases (C) | Estimated Incidence (C/Ss x 10,000) | Reported Incidence (Per 10,000 Students) |
|---|---|---|---|---|
| 11 | "2188[2407]" | "10[11]" | "45.7" | 45.7 |
| 10 | "2182" | "6[ 6]" | "27.5" | 27.5 |
| 9 | "2494[2244]" | "10[ 9]" | "40.1" | 40.1 |
| Total Estimated (Reported) | | "26" (26) | | Avg = 37.8 SD = 9.32 |
| 8 | "2312" | "8" | "34.6" | 34.6 |
| 7 | "2421" | "16" | "66.1" | 66.1 |
| 6 | "2578" | "14" | "54.3" | 54.3 |
| Total Estimated (Reported) | "7311" | "38" (38) | "51.7" unwt'd avg | Avg = 51.7 SD = 15.9 |
| 5 | "2535" | "18" | "71.0" | 70.9 |
| 4 | "2555" | "25" | "97.8" | 97.9 |
| 3 | "2765" | "24" | "86.8" | 86.8 |
| Total Estimated (Reported) | | "67" (67) | | Avg = 85.2 SD = 13.6 |
| 2 | "2544[2395]" | "17[16]" | "66.8" | 66.8 |
| 1 | "2734[2604]" | "21[20]" | "76.8" | 76.8 |
| Total Est. G 1&2 | "5278[4999]" | "38[36]" | "72.0" | 71.8 |
| K | "1022[1208]" ~2700[~2500] | "11[13]" | "107.6" [~41{52}] | 107.6 |
| Total Estimated (Reported) | | "49" (49) | | Avg(2) = 71.8 SD = 7.07 [Avg(3) = 83.7 SD = 21.3] |
| TOTALS: Est. No. (Registered No.) | "28,330[28206" (27,749] | "180" (180) | | |

1. Guesstimates made presuming the total PDD number and reported incidence rates were okay.

[**Note:** This reviewer suspects that, *if properly corrected for under enrollment*, it would appear that the "under-registration-corrected" incidence rate for *Grade K* would be less than half the reported value – supporting the reality that, *excluding the suspect Grade K data point*, the reported *Grade 1* and *Grade 2* incidence data clearly indicates a PDD incidence decrease after 1996.]

Using the preceding approximations, this reviewer has constructed an *approximate* numbers and cases table (**see** "**Reviewer's Guesstimated Approximate 'Grade' Data**" table on the preceding page).

Given the reported total enrollment, it would seem that the reason the authors did *not* report the cases and total number of students for each grade is that their *Grade K* data point either:

**a.** Should *not* have been included in their analysis because:
  **i.** less than half of the students that could have been enrolled were, in fact, "*registered*" while
  **ii.** most of the PDD-diagnosed students in the grade-"K" age were actually enrolled, or
**b.** *Because of points* "**a–i**" and "**a–ii**," the incidence rate for *Grade K* should have been corrected for the number of students that could have been enrolled but were *not* enrolled in *Grade K*.

Based on these findings, the authors should either report the data for cases and students by grade and establish that that the numbers in each grade evaluated were about the same or, ***if*** *the enrollment for grade K is much lower than the enrollment for the other grades as the data seems to indicate*, **then,** the journal that published this paper should retract it until:

- The apparent misleading reporting is appropriately corrected and
- The authors apologize for their failure to accurately evaluate the data by
  - excluding the data point for *Grade K* or, *if a valid correction can be made*,
  - correcting it for the estimated number of students that could have been enrolled in *Grade K*, and
- *In either case*, the authors have inappropriately represented the data for *Grade K*.

Moreover, lacking any data on the total number of children age 5 to 16 in the province of Quebec or information about the equivalence of the vaccination uptake rates between a small percentage of the minority "*Anglophone children*" studied and the unstudied majority "Francophone" children, this reviewer *cannot* assess the applicability of these findings to the "*province of Quebec*" as a whole. [**Note:** In statistical terms, the sample size is neither sufficient in size nor *representative* of the population of children in the province of Quebec in grades K through 11. Because the sample is obviously not *representative* of the children in the province of Quebec, the authors cannot validly project the results found for the sample (expressed in terms of PDD incidence) to the prevalence of PDD in Montreal much less in all of Quebec as their statements clearly indicate that they have attempted to do.]

Thus, it is *not* appropriate to characterize the reported grade incidence rates as "*prevalence*" rates much less to extrapolate from these reported incidence rates seem in an English-speaking school district in Montreal to the city of Montreal or, *worse*, the "*province of Quebec*" as a whole.

Similarly, this reviewer finds that the authors' second goal, "*(2) estimate the prevalence of specific diagnostic subtypes within the PDD spectrum*," again seems only to have been met for the population studied and, *for the reasons cited previously*, *not*, *as implicit in the authors' statement*, for the "*province of Quebec*" as a whole *nor* for the "*prevalence*" of any PDD in the "*province of Quebec*".

Furthermore, the authors failed to provide the data for the PDD cases, total number of students of each age in each grade, or, *failing that*, to report the incidence rate and cases for each age group (enabling any reader to estimate the size for each grade) in their "***Table 1***" information.

Given the preceding realities, this reviewer finds that the authors failed to either appropriately state or address their third goal, "*(3) evaluate trends in prevalence rates in successive birth cohorts*."

All that these authors could accurately do from the data they report collecting is "*evaluate trends in*" incidence "*rates in successive*" grade "*cohorts*."

Moreover, in their attempt to reach their fourth goal, "*(4) examine the relationship, if any, between trends in autism rates and exposure to varying levels of thimerosal during the study period*," it appears to this reviewer that the authors:

- Failed to ensure that all of their data were unbiased or about equally biased to a small extent with respect to:
  - **a.** non-included cases in the grade range studied, and
  - **b,** persons of school age but *not* in school,
- Apparently, ignored the downward "trend" in the incidence rates found for grades 1 (66.8 per 10,000) and 2 (76.8 per 10,000) compared to the *estimated* average (92.4 per 10,000) for grades 3–4,
- Improperly included the *Grade K* PDD incidence value because the apparent number of students in grade K was seemingly less than half that in any other grade,
- Incorrectly modeled the data using a "linear increasing" model when the data pairs (grade and PDD incidence rate in that grade) clearly indicate that a piecewise linear model should have been used provided the biased *Grade 11* and *apparently biased Grade K data points* were omitted from the fitting, and
- *Neither* the *Grade 11* PDD incidence value (because, *as the authors state*, it is based on a significant adjustment in the number of the PDD cases included by excluding 10 PDD cases from the *Grade 11* total) *nor* the reported *Grade K* PDD incidence value (because it is apparently inflated by a significant under ascertainment in the number of students registered in *Grade K* but no parallel obvious under ascertainment in the number of PDD cases in the students "*registered*" in *Grade K*) should have been included in the modeling conducted by these authors.

Further, the study approach used was *not* suitable to address, much less shed light on, the authors' fifth goal, *"(5) examine the relationship, if any, between trends in autism rates and MMR vaccination uptake*."

Additionally, with respect to the authors' "(c)*ompared with previous research on immunization and autism, this study uniquely examines exposure to high levels of thimerosal*," this reviewer respectfully disagrees.

This reviewer notes that the initial studies by the CDC (the "Phase 0" and "Phase 1" studies by Verstraeten *et al*.) published on-line by SafeMinds and the applicable general population studies published by the Geiers before this study was reported both assessed high levels of exposure for much larger populations of individuals.

Finally, since the authors did *not* determine the actual vaccination status (0, 1 or 2 MMR doses) for each PDD case *nor* assess the effect, *if any*, of age, weight, health, and other factors at each vaccination date, the authors could *not*, *as they assert*, properly test "*for the effects of a 2-dose MMR schedule before age 2 years*."

To properly do this they would have needed, *in this reviewer's view*, to segregate the PDD cases and students having no MMR, 1 MMR and 2 MMR vaccinations into separate groups, somehow correct for the confounding differences in the level of Thimerosal exposure each PDD case received, and then compare the PDD incidence rates among the MMR groups so constructed.

However, these authors did *not* even attempt to do the requisite data analyses.

"**METHODS**

**Subjects**

In the province of Quebec, children are educated either in English or French schools. Schools belong to school boards that are also organized according to language. The largest school board for Anglophone children in Quebec is the Lester B. Pearson School Board (LBPSB), which provides education to individuals in the south and western parts of the greater Montreal area. The LBPSB has 55 schools (45 elementary and 10 secondary) and provides education from kindergarten through grade 11. October 1, 2003, was chosen as the survey date. As of October 1, 2003, a total of 27749 children were registered within the LBPSB."

At a minimum, the authors' reporting should have stated or tabulated the total number of:

**a.** PDD cases in each grade and

**b.** Children in each grade

so that any reader could:

- Independently verify the grade incidence rates reported in the authors' figures and
- Ascertain that the populations in each class:
  - **i.** Were (or were *not*) about the same and
  - **ii.** *In general*, increased as the grade decreased.

"**Case Identification**

In Quebec, children with special education needs are either integrated, segregated within a regular school, or placed within a special school. Funding, in addition to the base grant received for all students, is provided to school boards when the special needs of a student are classifiable according to criteria established by the Ministry of Education of Quebec (MEQ). Of the 10 medical or psychiatric categories allowing the school to receive extra funding from the MEQ, PDD is one of the conditions that lead to the highest incremental funding. Each year, a list of children with identified PDDs attending any one of the schools within each of the province school boards is sent to the MEQ by September 30. Using this list, the MEQ determines the amount of extra funding each school board receives to meet the needs of children with PDDs. Until 2000, children with PDDs were administratively identified only if their diagnosis was specifically stated as autism (code 51). In 2000, the category was broadened to autism spectrum disorder (code 50). In addition, the LBPSB has a special support team to monitor the progress of children with PDD in its schools. This team keeps a list of children with a PDD diagnosis, which is updated on a weekly basis. The children with PDD who are the focus of this study were identified via this list. In grade 11, several subjects (N = 10) with a PDD diagnosis were aged 17 to 21 years, as by provincial law students with special needs can extend their secondary education up to age 21. Because the count of these older subjects could not be related to a meaningful denominator, they were excluded from the survey."

In general, this reviewer has no concerns about the information provided other than to note that no attempt was made to ascertain the number of "*Anglophone*" PDD cases, if any, that were located in the "*LBPSB*" service area who, *for whatever reasons*, were *not* attending an "*LBPSB*" school.

While the authors' adjustment of the *Grade 11* PDD cases may be valid, this reviewer notes that the authors did *not* report adjusting any of the other grades by relocating "overage" PDD children registered in a given "*LBPSB*" grade to their most age-appropriate grade.

Because no "*meaningful denominator*" could be constructed for all the PDD children "in" *Grade 11*, the authors should have, *in this reviewer's view*, simply excluded *Grade 11* from their study instead of trying to "correct" the PDD cases found there by excluding those 17 and older.

"**Data**
Children with a diagnosis of PDD were identified by school personnel and given a study code to preserve the anonymity of the data. Children's diagnoses were not verified by direct assessments, but it is worth noting that a majority of these children (N = 155; 86.1%) have been diagnosed at the Montreal Children's Hospital. School personnel further identified the diagnostic subtype using Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) diagnostic criteria, age, grade, and school the child was attending. When available, place of birth was recorded as well. Individual immunization data were not available for study subjects. Denominators used for further prevalence calculations were obtained through the LBPSB and included the total number of children (male/female) in each grade registered in any of the schools at the LBPSB. Thus, prevalence rates could be computed for each grade by dividing the number of children with a PDD diagnosis in a given grade by the corresponding denominator. Age-specific prevalence rates could not be precisely derived, because the dates of birth were only available for the PDD children but not for the whole school population."

Since the authors admit that the age information was *not* available for all the children in these schools, then the "***Year of birth***" information on the authors' "***Figure 1***" and "***Figure 2***" is, *at best*, misleading and, *as such*, should *not* have been included in the figures.

"However, we estimated the birth year of the entire school population based on their grade attendance. Thus, children in kindergarten were assumed to all be born in 1998, children in grade 1 in 1997, and so forth. We performed a check that this imputation method was correct by examining the correspondence between grade and year of birth using dates of birth from the PDD sample. In 9 of 11 comparisons, the mode of year of birth of the sample coincided with the estimated year of birth, providing confidence in our method. Although this method is not entirely accurate, the trend analysis was not influenced by potential birth cohort misclassification, as shown below."

This reviewer again notes that the authors' attempted rationalization for their "estimation" of "*the birth year*" is, *as their own comparisons reportedly showed in 2 of the 11 grade comparisons made*, **a)** inappropriate and **b)** "knowingly" somewhat misleading when it comes to the real years of birth for children in a given school grade.

For example, in *Grade K* and in grades 1 through 3, children presumed to be of an age to have received lower levels of Thimerosal may have, in fact, been a "year" older and received the higher level of Thimerosal exposure or, *when a child had skipped a grade in*

*this set*, been a "year" younger and received a lower level of Thimerosal, though the grade is presumed to have received the higher level of Thimerosal.

"**Immunization Exposure Data**
In Quebec, the schedule of immunization is defined by the Ministry of Health and Social Services.[45–49] Immunizations are administered by general practitioners, family doctors, and pediatricians in both community clinics and private offices and at no cost for the family."

While this reviewer has no problem with what the authors state, this reviewer notes that the authors failed to mention the other Thimerosal-preserved vaccines that, though *not* a part of the ministry's free "*schedule of immunization*," were nonetheless available for and administered to many Quebec children up to the age of 16 during the 1990s, including a Thimerosal-preserved hepatitis B vaccine and, *in some cases*, a Thimerosal-preserved influenza vaccine.

"**Vaccine Coverage**
Vaccine coverage has traditionally been very good in Quebec.[50] Several surveys have been performed in Quebec to evaluate the extent of adequate vaccine coverage among young children in Quebec. The definition of adequate vaccine coverage has varied between surveys, reflecting changes over time in the immunization schedule. Adequate vaccination was usually defined as the appropriate number of diphtheria-tetanus toxoids-pertussis, polio, Haemophilus influenzae type b (Hib), and MMR vaccine doses received by 24 to 30 months of age. Rates of adequate vaccine coverage have typically varied between 85% and 90% as illustrated by adequate coverage of 85.2% in 520 children aged 24 to 30 months,[51] of 87.7% among children aged 24 to 30 months born in 1989 and 1990,[52] and of 89.8% in 1270 children aged 24 months.[53] Thus, the vast majority of children born in Quebec are adherent to the official immunization schedule.[54]

Since: **a)** these data clearly indicate that probably *not less than* 10% of the children in Quebec were *not* vaccinated and **b)** vaccination is *not* required for school attendance, the authors should have excluded these children from the school populations in each grade unless there were children with a PDD diagnosis in the unvaccinated group.

Moreover, the authors should have, if possible: **a)** estimated the PDD incidence in the unvaccinated children if there were such or **b)**, if there were *not* any such, reported that fact for the unvaccinated population in each grade.

Further, the authors' failure to address the Quebec children vaccinated for hepatitis B and/or, if any, directly or indirectly given the Thimerosal-preserved inactivated influenza vaccine again misrepresents their Thimerosal-exposure findings by an unknown but possibly knowable amount – had the authors from the school district straightforwardly requested this information from the parents.

"**Thimerosal/Ethylmercury Exposure**
The schedule of immunization in Quebec and its changes over time can be consulted from public health official documentation.[45–49] From 1985 to 1987, a combined diphtheria, pertussis (cellular), tetanus vaccine was recommended at ages 2, 4, 6, and 18 months and 4 to 6 years. Each dose contained 50 µg of thimerosal (ie, 25 µg of ethylmercury), leading to a cumulative exposure of 100 µg of ethylmercury by age 2. In 1988, a Hib vaccine was added to the schedule at 18 months of age. Because each dose contained 50 µg of thimerosal, the cumulative exposure to ethylmercury from 1988 went up to 125 µg by age 2 years. In 1992, the immunization schedule recommended that the Hib be administered at 2, 4,

6, and 18 months, with each dose containing 50 µg of thimerosal. Thus, from 1992, the cumulative exposure to ethylmercury by age 2 years reached 200 µg.

From 1987 to 1995, the polio vaccine was administered separately at 2, 4, and 18 months and 4 to 6 years. The polio vaccine did not contain any thimerosal. In 1996, the polio vaccine and the Hib vaccine were combined with diphtheria, pertussis (cellular), tetanus vaccine in a thimerosal-free pentavaccine administered at 2, 4, 6 and 18 months of age, with a polio, pertussis (cellular), tetanus booster (thimerosal-free) at 4 to 6 years. From 1998 onward, the acellular pertussis vaccine replaced the cellular vaccine in the combined vaccine. Thus, from 1996 onward, all immunizations were thimerosal-free, leading to a nil cumulative ethylmercury exposure through vaccinations by age 2 years."

As previously discussed, the factual evidence clearly shows that the authors' "*Thus, from 1996 onward, all immunizations were thimerosal-free, leading to a nil cumulative ethylmercury exposure through vaccinations by age 2 years*" is an unsupportable claim because a Thimerosal-preserved hepatitis B vaccine was introduced the 1990s and given to a significant portion of Quebec's newborns and middle-school children.

Since a Thimerosal-free hepatitis vaccine was *not* licensed in Canada until 2001, some children in Grade K through 2 received between 25 µg and 75 µg (or more µg) of Thimerosal from the Thimerosal-preserved hepatitis B vaccine by age two (or later).

Further, the human influenza vaccines of this era were also Thimerosal-preserved and some grade "K–2" children may have received 12.5 to 25 µg, or more, of mercury from the Thimerosal-preserved influenza shots they received by age 3.

In addition, pregnant Canadian women receiving gammaglobulin drugs and, *in some instances*, a Thimerosal-preserved influenza vaccine may have transferred up to 80% of the dose of Thimerosal they received to their fetuses – from the 25 to 100+ µg of Thimerosal that the mothers may have received during pregnancy (ca. 20 to 80+ µg of Thimerosal to their fetuses, who would have weighed significantly less than a newborn baby).

This study *neither* addressed *nor* attempted to account for the impact from any of these Thimerosal sources.

"In addition, from January to March 1993, a mass immunization campaign against meningococcal disease was performed among subjects aged 6 months to 20 years.[55] In 10% of the cases, the vaccine used contained 50 µg of thimerosal. Therefore, in a small proportion of children, the cumulative exposure to ethylmercury by age 3 may have reached 150 (instead of 125) µg of ethylmercury in children born from March 1990 to December 1991 and 225 µg of ethylmercury in children born from January 1992 to September 1992."

This reviewer has no problem with what these authors report here but notes that the authors should have attempted to determine the total mercury exposure from Thimerosal-preserved vaccines for each of the "*180*" diagnosed with a PDD and reported their findings, but they did *not*.

Had the authors done this, their findings could have clarified the cumulative mercury exposures the PDD cases actually received, when they received the mercury (*in utero* or later) and the level of exposure at each vaccination time point.

From this actual exposure data, the authors may have been able to see the correlation, *if any*, between exposure amount and/or pattern and the actual PDD diagnosed and/or its degree of severity.

"**MMR Immunization**
MMR was incorporated in the official schedule of immunizations of Quebec in 1976. The recommended age for administration of MMR was 1 year of age up to 1996. Since 1996, the recommendation was to administer 2 MMR doses, at 12 and 18 months of age. Data on MMR uptake for the study period were available through the Direction de Santé Publique de la Capitale Nationale (N. Boulianne, BN, MSc, written communication, 2005). These data were routinely collected in the region of Quebec among 5-year-old children attending kindergarten during the years 1993-2004 (ie, for birth cohorts from 1988–1998). Vaccination records from children were used as the main source of information to document MMR vaccination and its date. When this information was not available, vaccination status of the children was obtained through consultation of the regional vaccination registry or else through direct contact with doctor's practices, both from community clinics or private offices. Data were unavailable for 2 birth cohorts (1987 and 1997) during the study interval. Surveys were performed annually on a total population of 35643 children, with each annual sample fluctuating in size between 2234 in 1990 to 5914 in 1993. For the 10 birth cohorts with available data, the average MMR uptake in Quebec was 93.2% during the whole period, ranging from 91.3% in the 1992 birth cohort to 96.4% in the 1989 birth cohort."

Again, since at least 3 % to 5 % of the students probably did *not* receive an MMR vaccination in the period from 1987 through 1995 when one dose of vaccine was given and, after 1995, 7% to 8 % did *not* receive both MMR doses, it would again have been valuable to ascertain, for the "*180*" PDD cases, whether or not there were any PDD cases who did *not* get an MMR vaccination and, *for those who did*, whether or not the PDD diagnosis and severity, for a given level of mercury exposure, tracked the number of MMR vaccinations received (0, 1 or 2).

In addition, a multidimensional interaction matrix among the various mercury levels and exposures, MMR levels, and the PDD diagnosis and its severity could have been constructed and evaluated to ascertain the magnitude of the interaction effects and the major factor effects on the PDD diagnosed and the severity of the PDD diagnosed.

Yet, the authors again inexplicably failed to even attempt these analyses for the PDD cases identified.

"**Statistical Analysis**
Data were analyzed by using SAS 8.2 (SAS Institute, Cary, NC) statistical software.[56] A conventional P value of .05 was chosen as a criterion for statistical significance. Conventional statistical tests were used for categorical variables. 95% confidence intervals (CIs) for prevalence estimates were calculated using the hypergeometric distribution (Fisher's exact interval). To assess the relationship between prevalence estimates and thimerosal exposure data, prevalence estimates for each successive birth cohort were modeled by using the SAS Logistic procedure and the events/trials syntax.[57] Birth cohort and level of ethylmercury exposure for each birth cohort were used as predictor variables in modeling the data. Birth cohort was treated as a continuous predictor. Level of ethylmercury exposure was used either as a continuous or a categorical predictor. When used continuously, the ethylmercury level for each birth cohort was that obtained from the official immunization schedule (range: 0–225 µg). A categorical ethylmercury exposure variable was created with 3 levels (0 = zero exposure; 1 = medium exposure [ie, between 100 and 150 µg ethylmercury]; and 2 = high exposure [200 µg ethylmercury])."

This reviewer finds the authors statements here problematic for a variety of reasons including, but *not* limited to:

**a.** Incorrectly treating the grade data estimated (for the PDD students) and accumulated for the other students as "*Birth cohort*" data when, in fact it was "grade cohort" data.

**b.** Treating the "grade cohort" data as a "*continuous predictor*," when, in fact, it is a *not* a "*continuous predictor*" because there are, *for example*, no grades between *Grade 1* and *Grade 2*.

**c.** The failure of the authors to include the mercury exposure from all vaccines available and used on children in the schools' population as opposed to just those "*from the official immunization schedule*."

**d.** The incorrect creation of a "*categorical ethylmercury exposure variable*" with "*3 levels (0 = zero exposure; 1 = medium exposure [ie, between 100 and 150 µg ethylmercury]; and 2 = high exposure [200 µg ethylmercury])*," when the exposure is to organic mercury from Thimerosal and, based on the authors' "***Figure 2***" and the actual vaccines that children may have received, there were many possible levels of Thimerosal that a given child may have received with, *counting the hepatitis B vaccine*, not less than four general levels of *mercury* exposure, "< 120 µg," "<175 µg," ≤ 200 µg," and "> 200 µg."

**"**RESULTS

**Prevalence**

Of 27749 children enrolled in the LBPSB, a total of 180 children were identified with a PDD diagnosis. This translates into a prevalence of all PDD combined of 64.9 per 10000 children (95% CI: 55.8–75.0). Half of the children with PDD (N = 91; 50.6%) had a diagnosis of PDDNOS. Of the remaining 89 children (49.4%), 60 children (33.3%) had a diagnosis of autistic disorder, 28 children (15.6%) had a diagnosis of Asperger syndrome, and 1 child (0.6%) had CDD. The corresponding prevalence figures are: for autistic disorder: 21.6 of 10000 (95% CI: 16.5–27.8 of 10000); for PDDNOS: 32.8 of 10000 (95% CI: 26.4–40.2 of 10000); for Asperger syndrome: 10.1 of 10000 (95% CI: 6.7–14.6 of 10000); and for CDD: 0.4 of 10000 (95% CI: 0.0–2.0 of 10000). Table 1 illustrates the gender and age distribution by PDD diagnostic subtypes. Consistent with other studies, the data show a preponderance of males in the PDD sample (82.8%), translating into a 4.8:1 male/female ratio. Surprisingly, the male/female ratio was lower in the Asperger group than in the other 2 groups. The statistically significant age effect reflects the marked change in PDD prevalence and distribution of PDD subtypes over time (1987–1998)."

In general, this reviewer does *not* disagree with the statements made in this section other than to note:

**a.** The rate data values are incidence rate data – *not* prevalence data.

**b.** The number of children having "*a diagnosis of autistic disorder*" is reported as "*60*" here but as "*61*" in the authors' "***Table 1***" and in two other places in the text – this apparent discrepancy should be explained and, *where appropriate*, corrected.

**c.** The lower "male/female" ratio reported for Asperger group (0.679) is *not* surprising to this reviewer.

**d**. The effects observed are grade effects and *not* "*age*" effects as the authors again assert.

**e.** The short period of time in this study, the failure to report the subtypes data for all grades, and the confounding by the changes in level of Thimerosal exposure all

preclude this reviewer from agreeing with the authors about their views on "*the marked change in PDD prevalence and distribution of PDD subtypes*."

"> Place Holder for:
**TABLE 1** Gender and Age Distribution by PDD Diagnostic Subtypes

Figure 1 provides prevalence estimates calculated separately for each grade that are used here as a proxy indicator for birth cohort. There was an important variability in prevalence estimates by grade, with the highest prevalence of 107.6 per 10000 being observed in kindergarten (eg, youngest children born in 1998), and the lowest prevalence being of 27.5 per 10000 for grade 10, among children roughly aged 16 years. Prevalence was relatively steady for grades 8 through 11. Using logistic regression, a statistically significant effect on prevalence was found for birth cohort (odds ratio [OR]: 1.10; 95% CI: 1.05–1.15), suggesting an average annual increase of 10% in prevalence rate. Inclusion of quadratic terms for birth cohort did not improve the fit of the model, suggesting that the increase of prevalence was linear during the study period."

This reviewer has a problem with the reported PDD incidence data for *Grade K*, which seems to this reviewer to be an invalid assessment of the true PDD incidence rate because there appears to be a significant underascertainment in the number of children who could have attended "Kindergarten" but, for whatever reason, did *not*.

This reviewer also has a problem with:

- The use of grade as a "continuous" proxy for "birth cohort," and
- The authors' suggestion that there was "*an average annual increase of 10% in prevalence rate*" when, in fact, there was an apparent *inverse* incidence-rate relationship only between grade and PDD incidence rate for grades 4 – 10.

In addition, this reviewer also found that the *Grade 11* data point should have been omitted because the incidence in *Grade 11* was corrected by throwing out "over age" cases even though no such similar correction was made for any of the lower grades.

Further, *when the suspect Grade K incidence rate is excluded*, it is clear that, *on average*, the PDD incidence rate declined in *Grade 1* and *Grade 2* as compared to the maximum *Grade 3/4* average PDD incidence rate.

Moreover, based on this reviewer's analysis of the information provided and his rough reconstruction of the class sizes and incidences in all grades, it seems clear that the author's reported incidence in *Grade K* is at least twice as large as it should have been if, *as they should*, the authors had corrected the denominator to all of the children *eligible* for *Grade K* instead of the number enrolled in *Grade K* since attendance seems to be optional for *Grade K*.

Had the *Grade K* incidence data been properly corrected, then it is obvious to this reviewer that, for grades "K–10," a piecewise linear fit for grades "1–4" and grades " 4–10" should have been used as the fitting basis for the authors' properly corrected findings. [**Note:** The point for *Grade 11* should have been omitted because the class actually contains some students older by more than2 years (those 19 – 21) than the nominal age for that grade when, for grades 10–K there are probably no non-PDD children who are more than two years older than the nominal age for those grades (though, because of enrollment birthdates cutoff rules, up to 25 % of the children in each grade may be a year older than the nominal age for that grade). When the authors provide, as requested, the class sizes and PDD cases numbers for each grade, this reviewer will be to better ascertain what the "corrected" PPD incidence should have been for *Grade K*.]

Based on the omission, or approximate correction of, the *Grade K* PPD incidence value, it seems clear to this reviewer that, *when the Thimerosal-level was reduced*, the incidence rate for PDDs also dropped after the Thimerosal level dropped in spite of an approximate doubling of the MMR exposure (from 1 dose up through 1995 to 2 doses in 1996 and beyond).

**"> Place Holder for:**
**FIGURE 1** MMR vaccine coverage and PDD rates over time.

**Autism and Thimerosal**

Figure 2 charts prevalence estimates and thimerosal exposure levels for each birth cohort from 1987 through 1998. A visual inspection of the data indicates that PDD rates started to increase before the change from medium (1987–1991) to high (1992–1995) exposure levels, and, even more convincingly, it shows that rates continued to rise after total discontinuation of thimerosal (1996–1998)."

After:

- Reading that a correction was applied to the *Grade 11* data and discounting that point,
- Critically examining the data by groups, and
- Omitting the data point for *Grade K* because it is an *anomalous* and has an apparently low-population-enrollment-biased PDD incidence rate,

this reviewer's visual inspection of the *Grade 10* through *Grade 1* data, finds, *on average*, that the average PDD incidence rate

- Increases from *Grade 10* through *Grade 4* and
- Decreases from *Grade 4* through *Grade 1*.

Based on this visual inspection for the data points that *apparently* need no correction, the level of PDD falls after the level of Thimerosal declined even though the number of MMR doses was doubled.

"The highest prevalence rate was found in the 1998 thimerosal-free birth cohort. To assess this trend statistically, we first compared the average prevalence in thimerosal-free birth cohorts (1996–1998) to that of previous thimerosal-exposed birth cohorts (1987–1995). The results indicate a significantly (OR: 1.39; 95% CI: 1.01–1.92; P < .05) higher prevalence of PDD in thimerosal-free cohorts (82.7 of 10000; 95% CI: 62.0–108.0 of 10000) compared with thimerosal-exposed cohorts (59.5 of 10000; 95% CI: 49.6–70.8 of 10000)."

Until the problems with the data for *Grade 11* and *Grade K* are addressed, these points should be omitted from any analysis.

Moreover, the cohorts that should have been compared are the grade "3–4" cohort to the grade "1–2" cohort since:

- These respectively represent adjacent approximately equal-size cohorts,
- The first consists of individuals mostly vaccinated before the significant decrease in the maximum Thimerosal exposure and
- The second consists of individuals mostly vaccinated after the significant decrease in the maximum Thimerosal.

This reviewer also finds the authors' attempting to compare a wide-range cohort (grades 11-3) with a narrow-range cohort (grades 2-K) to be both scientifically unsound and somewhat reprehensible unless:

**a.** the incidence rate across both ranges is approximately constant (and it is obviously *not* constant for the authors' wide "grade 11-3" range) and

**b.** an appropriately population-weighted comparison is made (which the authors apparently did *not* do in this article).

Thus, besides an apples and oranges comparison with respect to the PDD incidence values, the authors improperly included biased data points (one of which they attempted to "correct" [the *Grade 11* PDD incidence rate] while both ignoring and apparently attempting to conceal the bias for the other [the *Grade K* PDD incidence rate]).

Based on the preceding realities, this reviewer call upon the authors to compute and report the odds ratio (OR) and their confidence intervals for the grade 4-3 cohort and the grade 2-1 cohort and to compare and explain those OR values or, *failing that*, to admit that their original comparisons were, *for the reasons stated*, inappropriate.

In addition, the use of "*birth cohort*" in place of "grade cohort" is also *neither* scientifically sound *nor*, *based on the authors' data*, appropriate for this epidemiological dataset.

"> **Place Holder for:**

**FIGURE 2** Birth cohort prevalence rates and ethylmercury exposure. Dotted lines take into account the additional ethylmercury exposure because of a mass vaccination campaign against meningitis (see text).

"Logistic regression modeling of the data was then performed. Because birth cohort was associated with both level of thimerosal exposure and prevalence of PDD, birth cohort was entered in the model to adjust for its confounding effect. We then added in thimerosal exposure to the model to evaluate its specific contribution to the trend in prevalence. When thimerosal exposure was used as a continuous variable, no significant effect was found (2 = 2.54; degrees of freedom [df] = 1; P = .11). Similarly, when thimerosal exposure was entered as a categorical variable, no effect of thimerosal exposure on rates of PDD could be found (2 = 3.24; df = 2; P = .20). In both models, birth cohort exerted a significant effect on prevalence rates (OR: 1.10; 95% CI: 1.05–1.15), and adequate fit was obtained (Hosmer Lemeshow 2 = 7.90; df = 10; P > .50). Thus, thimerosal exposure was unrelated to the increasing trend in PDD prevalence."

Since, *for the reasons discussed in detail*, the data points the authors used and their bases are *not* scientifically sound and the authors' model assumptions are obviously flawed, the findings reported by the authors here are, *of necessity*, *not* valid.

Hopefully, when the authors correct their biases and appropriately model the data, they will find what the data points (excluding the biased ones) clearly indicate, the PDD incidence rate, *not* "*PDD prevalence*" rate, is related to both the increasing and the decreasing level of Thimerosal exposure in spite of the confounding effect of a concomitant doubling of the MMR dosing when the level of Thimerosal exposure was reduced.

"We took several additional steps to assess the robustness of these results. First, to account for the slight increase of levels of thimerosal exposure for children included in the mass immunization campaign against meningococcal disease, we allocated new values of thimerosal exposure measured continuously for the 1990 and 1991 birth cohorts (150 μg instead of 125 μg) and for the 1992 birth cohort (225 μg

instead of 200 µg; see Fig 2). Because this did not affect our exposure categories, only analyses with the continuous thimerosal variable were repeated. The results remained unchanged with no statistically significant effect of thimerosal on prevalence rates of PDDs (data not shown)."

Since the basis data for this analysis include the same points that should have been excluded and used the same incorrect model, the results are as invalid as they were in the previous analysis.

Hopefully, when the authors ignore the biased PDD values for *Grade 11* and *Grade K*, and more appropriately model the data, they will find what the data points (excluding the biased ones) clearly indicate, the PDD incidence rate is related to both the increasing and the decreasing level of Thimerosal exposure in spite of the confounding effect of a concomitant doubling of the MMR dosing when the level of Thimerosal exposure was reduced.

"Second, because of the ecological nature of the data set, individual thimerosal exposure data were not known. However, places of birth were available on all 180 of the PDD subjects. Of the 180 subjects, 158 (87.8%) were born in Quebec and were, therefore, extremely likely to have followed the immunization schedule. The proportion of children born in Quebec did not vary across the $^{3}$ thimerosal exposure periods ($\chi^2 = 0.60$; df = 2; $P > .50$). Analyses were repeated on the subsample of Quebec-born subjects. Prevalence rate of PDDs increased from 40.6 of 10000 in 1987 to 102.5 of 10000 in 1998, the linear increase being statistically significant (OR: 1.10; 95% CI: 1.05–1.16; $P < .0001$). The PDD prevalence in thimerosal-free 1996–1998 birth cohorts (74.9 of 10000; 95% CI: 55.3–99.1 of 10000) was significantly higher (OR: 1.46; 95% CI: 1.04–2.05; $P = .031$) than that in thimerosal-exposed 1987–1995 birth cohorts (51.6 of 10000; 95% CI: 42.4–62.1 of 10000). Logistic regression models to test for the effects of thimerosal among Quebec-born subjects led to negative results similar to what was obtained in the whole sample. More specifically, when the effects of birth cohort were already accounted for, the effect of thimerosal was nonsignificant when treated either as a continuous exposure ($\chi^2 = 1.60$; df = 1; $P = .21$) or as a categorical exposure variable ($\chi^2 = 2.21$; df = 2; $P = .33$). In both analyses, birth cohort effects were significant (OR: 1.10; 95% CI: 1.05–1.16; $P < .0001$), and goodness-of-fit statistics were not significant, indicative of a good model fit."

Since the basis data for this analysis include the same points that should have been excluded and used the same incorrect model, the results are as invalid as they were in the first regression analysis.

Hopefully, when the authors restrict their evaluation to the *Grade 10* through *Grade 1* PDD incidence values and appropriately model that data, they will find what the data points (excluding the biased ones) clearly indicate, the PDD incidence rate for the Quebec-born English-speaking children in the one school district they studied in Montreal was related to both the increasing and the decreasing level of Thimerosal exposure in spite of the confounding effect of a concomitant doubling of the MMR dosing when the level of Thimerosal exposure was reduced.

"Third, whereas exposure data were precisely calculated for each birth cohort, our method of estimation of birth cohort was indirect, raising the possibility of some misclassification on exposure. To address this problem, we rescored the year of birth by either subtracting or adding 1. This created 2 new data sets (1986–1997 and 1988–1999) with which all of the above analyses were repeated, ascribing thimerosal exposure values of 100 µg for 1986 and of 0 µg for 1999. All of the results remained unchanged (data not shown)."

Since the basis data for this analysis include the same points that should have been excluded and used the same incorrect model, the results are as invalid as they were in the first regression analysis.

Hopefully, when the authors restrict their evaluation to the *Grade 10* through *Grade 1* PDD incidence values and appropriately model that data, they will find what the data points (excluding the biased ones) clearly indicate, the PDD incidence rate for the these minority English-speaking children was related to both the increasing and the decreasing level of Thimerosal exposure in spite of the confounding effect of a concomitant doubling of the MMR dosing when the level of Thimerosal exposure was reduced.

"Fourth, because some diagnostic misclassification could not be entirely ruled out and is more likely to occur with more atypical forms of PDD, such as PDDNOS or Asperger syndrome, we repeated the analyses on the subsample of 61 children with a diagnosis of autistic disorder. The results were similarly negative."

Since the basis data for this analysis include the same points that should have been excluded and use the same incorrect model, the results are as invalid as they were in the first regression analysis.

Hopefully, when the authors restrict their evaluation to the *Grade 10* through *Grade 1* "*autistic disorder*" incidence values and appropriately model that data, they will find what the data points (excluding the biased ones) clearly indicate, the PDD incidence rate for the children studied was related to both the increasing and the decreasing level of Thimerosal exposure in spite of the confounding effect of a concomitant doubling of the MMR dosing when the level of Thimerosal exposure was reduced.

"**Autism and MMR**

Vaccination uptake of MMR was high in Quebec, averaging 93.2% over the study years. Figure 1 illustrates the lack of relationship between PDD rates in birth cohorts from 1987 to 1998 and MMR uptake estimates. There was a slight but significant trend toward a decrease in MMR uptake from 1988 to 1998 (2 for trend = 80.7; df = 1; P < .001) with vaccine uptake dropping from 96.1% in the older birth cohorts (1988–1989) to 92.4% in younger birth cohorts (1996–1998). During the same period, a significant and linear increase in rates of PDD occurred (see above). Analyses were repeated on the subsample of 158 Quebec-born subjects who, considering the high MMR vaccine uptake in Quebec, were most likely to have been individually exposed to the MMR vaccination according to the official schedule of immunizations. As indicated above, prevalence rate of PDDs increased from 40.6 of 10000 in 1987 to 102.5 of 10000 in 1998, the linear increase being statistically significant (OR: 1.10; 95% CI: 1.05–1.16; P < .0001). Thus, PDD rates in Quebec-born children most certainly individually exposed to MMR vaccine increased at a time where MMR uptake decreased slightly, albeit significantly. As the schedule of MMR vaccination changed in 1996 with the addition of a second dose at 18 months of age, we performed 2 sets of analyses to assess whether PDD rates and MMR exposure were associated during the period of single MMR exposure only and to evaluate whether or not the introduction of a second MMR dose at 18 months of age from 1996 onward had any relationship with the trend in PDD prevalence. First, we examined the data after censoring the 1996–1998 birth cohorts to reassess the association within the context of a stable, single MMR dose exposure period. For the 1987–1995 birth cohorts, the increase in PDD rates still showed a statistically significant increase (OR: 1.15; 95% CI: 1.07–1.23; P < .001), whereas MMR vaccine uptake showed a small but significant downward trend during the corresponding interval (2 for trend = 97.5; df = 1; P < .001) from 96.1% in older birth

cohorts (1988–1989) to 92.2% in younger birth cohorts (1994–1995). Thus, the data did not support any association between the single MMR dosing at 12 months of age and the PDD rate in these birth cohorts. Second, to test for a change in the rate of increase of PDD prevalence after the introduction of the 2-dose schedule in 1996, we performed 2 separate analyses. We modeled the prevalence data with multiple logistic regression using birth cohort (continuous), period (1987–1995 and 1996–1998), and the corresponding interaction term as predictors. In this model, the hypothesis of a change over time in the rate of increase of PDDs before and after 1996 is tested by evaluating the interaction term in the model. This interaction term was nonsignificant (Wald 2 = 3.14; df = 1; P > .05), suggesting no difference in the upward trend before or after 1996. Then, we used the 1987–1995 prevalence rate series to predict what would be the prevalence estimates for the subsequent 3 years assuming that the linear increase in PDD rate observed from 1987 to 1995 remained constant. The predicted values and their associated 95% CIs for PDD rate were 108.1 of 10000 (83.41–139.86 of 10000), 123.8 of 10000 (91.01–168.14 of 10000), and 141.8 of 10000 (99.10–202.4 of 10000) for the years 1996, 1997, and 1998, respectively. Jackknife cross-validation showed very good robustness of the prediction model (data not shown). All of the actual observed prevalence estimates for these years fell below the predicted values, and in 2 instances (years 1996 and 1997), the observed prevalence estimates fell outside the predicted confidence limits. Thus, these combined results showed no indication that PDD prevalence in the 2-MMR dosing period had surpassed the values expected from the trend estimated from the single-MMR dosing period. Finally, we restricted our trend analysis to the 61 subjects with an autistic disorder diagnosis to evaluate the effects of potential diagnostic misclassification. In this subsample as well, a significant prevalence increase occurred from 1987 to 1998 (OR: 1.23; 95% CI: 1.13–1.34) at a time where the MMR uptake was decreasing significantly (see above). Thus, taken altogether, no association between MMR vaccinations (both 1 or 2 doses) and autism or PDD rates was suggested by these data."

Since, as this reviewer has discussed, the study design is *not* valid, the results and findings reported here are similarly *not* valid.

To establish that there was no MMR effect, the authors would have needed data where the level of Thimerosal was a constant and, at random, about one-third of a significantly sized population received 2 MMR doses, one third of that population only received 1 dose, and the remaining third received no MMR vaccination.

Then, one could have looked at the excess rates, *if any*, of PDD incidence or distribution (more autistic disorder) in the doubly dosed children as compared to the singly dosed children and the unvaccinated children and determined the magnitude of the MMR dosing effects, *if any*, on the PDD incidence or distribution.

Unfortunately, in this case, when the MMR does was doubled, the level of Thimerosal was significantly reduced making it hard to estimate the effect because, *given the PDD incidence variabilities reported*, the population is probably too small to reliably determine the effect of increasing from one to two doses of the MMR vaccine and there are probably *not* enough students in this population who received the Thimerosal-preserved vaccines but did *not* receive at least one MMR vaccine dose.

**"**DISCUSSION

**Prevalence**

The PDD prevalence estimate in this study was highly consistent with most recent surveys performed in several countries.[6,7,10] This high figure was unexpected, because surveys that rely solely on

administrative sources for case identification (e.g., medical or educational records) usually yield lower prevalence estimates.[7] Moreover, the rate in the 1998 birth cohort was >1% although the lower-bound limit of the CI was in the 0.6% to 0.7% range."

As this reviewer has previously discussed, the *Grade K* cohort, mislabeled the "*1998 birth*" cohort by the authors seemingly has an under-enrolment-biased PPD incidence, not "*PDD prevalence*," because it appears that about half or less of the children eligible to enroll did enroll but that most all PDD cases enrolled because the schools provide badly needed support to the parents of those with PPD children.

This reviewer estimates that the appropriately corrected PDD incidence is on the order of 40 to 50 per 10,000 and not the author's reported "*107.6 per 10000*" value.

"Several factors could have influenced the prevalence in our study. First, diagnosis could not be directly confirmed, and it is therefore possible that PDD diagnoses were overused leading to diagnostic misclassification and overestimation of the prevalence. However, a large proportion of subjects included in this survey had been assessed and diagnosed in our pediatric hospital by different qualified professionals, limiting the extent of that possibility. In addition, the pattern of PDD diagnostic subtypes and gender correlates was fairly typical of other published samples."

This reviewer can only agree with the authors that the observed PDD incidence rates for *Grade 10* through *Grade 1* were *not* assessment and diagnosis biased.

Since the individual data for the "*PDD diagnostic subtypes*," including cases and students in each grade, were *not* provided, this reviewer *cannot* comment on their pattern or their correlation with other published data.

"Second, special schools in Montreal that provide services to children with mental retardation, sometimes associated with PDD, were not included in the study, leading to a potential underestimation of the true population rate. However, because the school board has a policy of integration of children with even severe handicaps, especially at a young age, the magnitude of this downward bias likely remained small."

Absent any data on the numbers and ages of those PDD cases in these special schools, this reviewer can only agree that the authors' estimates are underestimates of the true incidence except possibly for the author's *Grade 11* and *Grade K* PDD estimates.

"Third, because the school board is known for its inclusive and supportive approach for children with PDDs, it is possible that parents of children with PDDs may have migrated to the geographical catchment area of the school board to provide their children with better educational opportunities. Unfortunately, data about places of residence before registration to school were not available, precluding us from assessing whether selective migration into the local area by parents of children with PDDs might have occurred. The extent to which the previous possible biases cancel each other out cannot be gauged."

This reviewer finds that the authors' statements here seem to be reasonable and to accurately reflect the reality they have described.

"Nevertheless, the estimate of 65 of 10,000 is highly consistent with other recent studies and shows that PDDs are relatively frequent disorders among children. Also, when PDDs were broken down by subtypes, a fairly typical pattern emerged with the prevalence of PDDNOS being 1.5 times higher than

that for autistic disorder, and the prevalence of CDD being extremely low, consistent with available estimates.[7] Our PDD rate cannot be directly compared with the only previous Canadian study,[44] because the 2 surveys differed in their case definition and methods of case ascertainment."

Except for the misuse of the term "*prevalence*," this reviewer has no problems with the authors' statements here.

"There was a statistically significant trend for increasing prevalence rates in younger birth cohorts (as indexed by grade attendance). On average, the prevalence rate increased by 10% annually over the 12 years of the study."

This reviewer finds that the authors' assertions here are *not* substantiated by the data they report when the values for *Grade 11* and *Grade K* are excluded.

Excluding the data from *Grade 11* and *Grade K*, the data indicate that PDD incidence rate, by grade,

- Increased by about 11 cases per 10,000 per grade as the grade decreased from *Grade 10* (where the average incidence rate was about 33.5 cases per 10,000) to *Grade 4* (where the reported PDD rate was 97.9 cases per 10,000) and
- Then decreased by about 9 cases per grade as the grade continued to decrease from *Grade 4* to *Grade 1* (where the estimated average PDD rate is about 71.8 cases per 10,000).

If the reviewer's *estimated corrected PDD-incidence value* for *Grade K* were to be included, the average decrease in the incidence rate for PDD cases would further drop from the *Grade 1* average estimate of about 71.8 PDD cases per 10,000 children to this reviewer's corrected Grade K guesstimates of about 40 to 50 cases per 10,000 children, or a decrease of about 20 to 30 cases per 10,000 children.

The declining PDD incidence rates for Grade 4 through Grade 1and the estimated "corrected" Grade K incidence clearly indicate the removal of several Thimerosal-preserved vaccines in 1996 has had a significant effect on reducing the PDD incidence rates for children mostly born two to three years, or later, after several Thimerosal-preserved vaccines were replaced by a single combined Thimerosal-free vaccine.

"This finding is consistent with trends in other studies that have repeatedly shown increasing prevalence rates in younger birth cohorts in the last 15 years.[14,15] It cannot be concluded from this data whether a genuine increase in the incidence of the disorder in the population occurred during the study period, or increased ascertainment and broadened diagnostic criteria, or a combination of both factors applied."

This reviewer finds that the authors' remarks here are at odds with the realities contained in the data.

Moreover, since there were no significant changes in "*ascertainment and broadened diagnostic criteria*" from 1994 onward, and the PDD incidence rates, *not* "*prevalence rates*" (as the authors assert), appear to have decreased for the children born in 1996 and later, this reviewer suggests that the authors need to revise their remarks here.

"Nevertheless, 4 factors can be identified that may have given rise to this trend. First, new nosographies and diagnostic criteria were introduced in 1992 with International Classification of Diseases, 10th Revision,[58] and in 1994 with DSM-IV,[1] that broadened the category of PDD. The most obvious example is the introduction of the entirely new category of Asperger syndrome in both diagnostic

schemes, a diagnosis that did not exist previously. The direct impact of using different diagnostic criteria on prevalence estimates has been well illustrated in a Finish study[59] where a twofold to threefold increase in prevalence resulted from applying old or new diagnostic criteria to the same survey data and subjects. Second, more expertise in diagnosing autism developed in the area with the establishment in recent years of a strong autism spectrum disorder clinical program at the Montreal Children's Hospital, the tertiary pediatric care institution that delivers services to Anglophone children. Third, a policy change at the MEQ level occurred in the summer of 2000 wherein the special education code 50 (PDD, as per DSM-IV) replaced the code 51 (autism, as per Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition) that had been in place for about a decade to identify PDD children with special needs and to provide additional funding for the schools.[60] This change made the new special education code pertaining to children with autism broader and applicable to a greater number of children, especially those diagnosed with either Asperger syndrome or PDDNOS who subsequently became eligible for extra support. Fourth, in 2000, because of initiatives related to autism already underway in the board, the LBPSB received the Center of Excellence for Autism recognition from the MEQ. This afforded the board the opportunity to further develop their expertise in diagnosis, treatment, and inclusion of students with PDDs, as well as required it to be a resource to the other Anglophone boards in the province. Combined altogether, these factors account most certainly for the upward trend in diagnoses in successive birth cohorts, although it is not possible to definitely rule out other explanations.[7] It is of interest that similar factors (broadening of diagnostic criteria and changes in policy with the 1990 revision of the Individuals with Disabilities Educational Act) have been hypothesized by several authors to explain upward trends in rates of PDDs in recent US studies.[13–15,61,62] With rates of 0.6% to 0.7%, PDDs are among the most prevalent conditions impairing young children's lives, translating to >50000 Canadian children below age 20 years in need of services.

> Except for the authors' closing statement, "*With rates of 0.6% to 0.7%, PDDs are among the most prevalent conditions impairing young children's lives, translating to >50000 Canadian children below age 20 years in need of services*," the authors need to significantly revise their remarks because it is clear (from the "minimally" biased PDD data [in *Grade 10* through *Grade 1*]) that the PDD incidence in children born in or after 1996 (most of the children in grades 2 and 1) clearly decreased from the highs seem in those children born before 1996 in 1993, 1994, and 1995 when Thimerosal exposure was at its peak in Canada.

"**Thimerosal and Ethylmercury Exposure**
During the 12 years encompassed by our study, thimerosal exposure before age 2 of each birth cohort changed several times and ranged from nil to a high value of 225 µg."

> Based on the Thimerosal-preserved hepatitis B (given from birth) and influenza vaccines that, *though they were given to children in the 1990s*, the authors neglected to address, the maximum level of mercury exposure from Thimerosal-preserved vaccines given to children 2-years old and younger probably ranged from < 100 µg to < 300 µg in the period covered by the author's studies.

"This provided a unique opportunity to test the relationship of ethylmercury exposure with rates of PDDs, free of a known problem of vaccine safety studies when high rates of exposure in populations, and therefore low variability in exposure, constrain the data and limit the opportunity to detect effects.[63] No association between thimerosal levels treated either continuously or categorically with PDD rates could be found in our study. In fact, it was remarkable that the PDD rates were at their highest value in birth cohorts that were thimerosal free, providing a clear and convincing message on the lack of an association. The results were robust and held true when various analyses were conducted to evaluate the

potential impact of misclassification on exposure and diagnosis. Within each period of medium, high, or nil exposure, the same trend toward a steady increase in PDD rate was observed, demonstrating total independence of the 2 variables. Our results are entirely consistent with cohort,[30–33] case-control,[64] and other ecological studies performed in Denmark and Sweden.[34,35] It is worth emphasizing 3 particular features of our results. First, because we were aware of limitations of ecological data, we performed complementary analyses on the subsample of Quebec-born subjects, a group with a very high probability of having been individually exposed to the official vaccination schedule of their birth cohort. The results remained unchanged. Second, the PDD rate in our study was high and consistent with recent epidemiological estimates coming from the United States[65] and the United Kingdom.[9] Thus, the convergence of our findings with those of the 2 ecological studies from Scandinavian countries[34,35] suggests that the lack of association reported by these authors was not because of the lower prevalence of PDDs reported in their respective investigations. Third, exposure to ethylmercury in some birth cohorts of our study reached levels as high as those that were attained in the US immunization schedule in the 1990s and were higher than those ever reached in the United Kingdom and Scandinavian populations. Thus, the lack of association between PDD rate and high thimerosal exposure found in our study provides new evidence on the absence of an association between autism/PDD and high exposure levels to ethylmercury that is relevant to the North American public."

Since the "unbiased" data reported by the authors in *Grade 10* through *Grade 1* clearly show a relation between maximum Thimerosal level and PDD incidence by grade cohort, the authors' remarks here should be ignored because they are based on a false premise.

"**MMR and Autism**

During the 11-year interval encompassed in our study, rates of PDD significantly increased, whereas MMR vaccine uptake showed a slight opposite trend. This finding is consistent with several other ecological studies that have tested an association between MMR vaccine uptake and rates of autism or PDD in the United Kingdom,[21,23] in Japan,[66] in Sweden,[67] and in the United States.[22] In this study, we were able to restrict the analysis to Quebec-born subjects who were most certainly individually exposed to MMR in light of the very high MMR uptake in Quebec throughout the period (93%). Thus, the usual limitations of ecological studies because of lack of information on individual exposure might not have applied to our study. It is also noteworthy that the MMR vaccine uptake actually declined in the study period, whereas the rates of PDD went up, both trends being significant. The opposite directions of both trends make it even less likely that a true association was not detected in our data. This, too, makes it less plausible that a positive association applying only to a small subset of PDD children would have gone unnoticed. Moreover, the change in the MMR schedule of immunization with the introduction of a second dose by the age of 18 months occurring in 1996 gave us opportunities to examine the effects of a 2-dose MMR schedule in infants. First, we established that the lack of association between MMR uptake and PPD rates applied to the period (1987–1995) where a single MMR dose was administered at 12 months of age. Thus, rates of PDD were rapidly increasing well before the introduction of the 2-dose schedule and, during that first phase, the increase of PDD rate bore no relationship with MMR vaccine uptake. Second, we tested whether the introduction of a second MMR dose after 1995 accelerated the increase in PDD rates in the following 3 years. No statistically significant difference could be found between the rate of increase in PDD prevalence between the 1-dosing and the 2-dosing periods. In fact, the end point prevalence estimate for 1998 was consistent with the value predicted on the basis of the 1987–1995 rate of increase. Therefore, 1 conclusion of this study is that 2-dosing schedule with MMR before age 2 is not associated with an increased risk of PDD."

As this reviewer has previously established, the authors *cannot*, *from this data*, make any valid assertions about the effect of MMR vaccination on the observed PDD rates because it is confounded by the significant nearly concomitant decrease in the level of maximum Thimerosal exposure.

Based on this reality, the authors' remarks here should simply be ignored.

"**Limitations**
Several limitations of our study must be acknowledged. First, we relied on administrative codes for the diagnosis of PDDs, and children could not be individually assessed for diagnostic confirmation. Nevertheless, the majority of children attending this school board with a PDD diagnosis were diagnosed in the tertiary medical center where one of us (E.F.) leads a specialized assessment team, and, therefore, the diagnostic assessment of this sample should be viewed with confidence in many cases. Also, results remained unchanged when we restricted the analyses to subjects with a stricter diagnosis of autistic disorder, a subsample where diagnostic misclassification is unlikely to be occurring. Second, the study cannot control for whether or not the high number of children with PDDs identified in this survey reflects migrations into the schools from this particular school board that are known to have a proactive policy of integration and support of children with PDDs. If families of preschoolers were to change residence to access the schools within the LBPSB for their child's education, this might inflate the number of children with PDD in this school board. To test this hypothesis, data from other school boards should be obtained, and knowledge of the residence of the family at birth and before school entry could also help to address this issue. Unfortunately, this information was not available in the survey data that we could obtain. However, it is worth noting that if such migrations occurred, it might bias our prevalence estimates but would have no impact on the thimerosal and MMR analyses, because migration into the area must be independent of vaccination history. Third, data about regression in the course of the development of children with PDD were not available in this study, precluding us from assessing risk associations with immunizations specifically for this subgroup. Nevertheless, the claim that only this PDD subtype would be sensitive to thimerosal exposure cannot be supported, because a significant increase of PDDs continued in Montreal after total discontinuation of thimerosal, providing strong evidence that thimerosal does not increase the risk of PDD and, indeed, of any PDD variant. If thimerosal exposure was associated with an increase in the risk of the regressive subtype of autism (thought to apply to 20% of PDD cases[24,68]), then, at the very least, a slowing down in the upward trend in PDD rates should have been observed after 1996 when thimerosal was entirely removed from vaccine preparations. This was not observed, and the upward trend continued in a linear fashion. Rates of PDDs were, in fact, higher in the thimerosal-free birth cohorts than in any preceding period where exposure to thimerosal was at either medium or high levels. With respect to MMR, the claim of a putative "autistic enterocolitis" regressive phenotype has already failed to be supported in other studies,[24,69] and epidemiological studies have shown that the regressive phenotype of autism has not increased over time.[24,69,70] Given this, our findings of a regular increase in PDD and autistic disorder prevalence while MMR vaccine uptake was decreasing during the study period are not consistent with any increase in the risk of PDD, regressive or not, that could be attributed to MMR."

In general, *for the reasons stated in this reviewer's previous in-depth commentary*, most of the authors' remarks here should also simply be ignored.

"**Implications**
There are several important implications of this study. First, our study adds additional evidence deriving from a large, population-based survey that PDDs are one of the most common developmental disorders in young children. With a prevalence of 0.6% to 0.7%, the service implications are straightforward.

Second, as in other recent studies, factors such as broadening of diagnostic criteria, improved awareness about the disorder, changes in official social and educational policies, and improved access to services are certainly the primary driving force underlying the increasing prevalence figures.[7] Yet, the possibility that a real change in the incidence could have occurred as well cannot be definitely ruled out from existing data. Third, our findings clearly failed to detect any relationship between thimerosal exposure and rates of PDDs. These findings concur with those from other similar ecological investigations[34,35] and of more controlled epidemiological studies.[25,38] Previous negative studies, especially those conducted in European countries, have sometimes been criticized on the account that either the rates of PDDs were not as high as those in North America, that the cumulative exposure to thimerosal was much lower than that attained in the United States in the 1990s, or both. This study avoids both pitfalls and is, therefore, very informative for the North American public. In addition, the rate of exposure varied from nil to very high levels of vaccine-derived ethylmercury, allowing us to test for effects along the full range of exposure and to detect possible threshold effects as well. All of the results were negative. Fourth, as in previous studies,[25] no effect of MMR vaccine could be detected on the risk of PDD. The trends went in opposite directions, making it unlikely that even small effects applying to a small subset of children would exist. Furthermore, this study added new evidence suggesting that the 2-MMR dose schedule before age 2 years also had no impact on rates of PDD. Fifth, parents of children with PDD and the general public should be made aware of the consistency of negative studies on the 2 hypotheses linking risk of autism and immunizations. Children with autism and their younger unaffected siblings should be vaccinated. Unvaccinated children are at much higher risk of contracting measles and suffering from its sometimes severe or lethal complications.[71] There is no evidence for an epidemiological association between ethylmercury and autism and no scientific basis for using chelation therapies, which can be dangerous. Decreasing MMR uptake in the British isles has led to more frequent measles outbreaks of greater magnitude[27] and to children's deaths.[72] Findings of negative studies are, indeed, more difficult to convey, but, here, the evidence lies in the striking convergence of studies accumulated by different groups, with different designs and in different places."

Since the minimally biased data for *Grade 10* through *Grade 1* clearly support a link between PDD incidence and Thimerosal exposure level, the authors' statements concerning the lack of a link between maximum organic mercury exposure from Thimerosal-preserved biological products and PDD incidence should be ignored.

Moreover, because of the confounding between increased MMR dosing (2 doses) and decreased Thimerosal-derived organic mercury exposure by age 2 (< 100 µg) as compared to the baseline 1 MMR dose and, on average, > 150 µg Thimerosal-derived organic mercury exposure by age 2, this data *cannot* be expected to shed much, if any, light on the relationship between PDD incidence and the number of MMR vaccine doses in the presence of the direct and indirect (in utero) exposure to Thimerosal-containing biological products, including Thimerosal-preserved vaccines and gammaglobulins.

To conduct a valid "worst case" study, the authors would have needed to conduct a double blind study of a population of not less than about 60,000 children who all received a significant Thimerosal dose (> 150 µg by age 2) and, at random, 1/3$^{rd}$ were given two placebo injections (1 at 12 months and 1 at 18 months of age), 1/3$^{rd}$ were a MMR at 12 months and a placebo at 18 months and the last third received 2 MMR doses (1 at 12 months and the other at 18 months) with all other non-Thimerosal-preserved vaccines postponed until the child was at least 21 months of age.

Based on the children studied and their putative vaccination exposures, the authors' indirect studies could *not*, *for the reasons stated*, be expected to shed any scientifically sound light on the link between the MMR vaccine and PDDs.

## "ACKNOWLEDGMENTS

Dr Fombonne's salary support is partially funded through the Canada Research Chair Canadian Institutes for Health Research (to Dr Fombonne and McGill University).

We are indebted to Dr Monique Landry from the Direction Générale de la Santé Publique of Montreal, Ministère de la Santé et des Services Sociaux, for her assistance in obtaining precise data on the immunization schedules in Quebec and to Nicole Boulianne de la Direction de Santé Publique de la Capitale Nationale for providing data on MMR uptake surveys."

This reviewer has received no funds from any source to conduct this assessment of the study and results reported here.

However, this reviewer is indebted to Dr. Mark R. Geier, David A Geier, and Dr. Gary S Goldman for their advice in how to proceed with the query for the minimum unpublished data required to evaluate the basic results reported, the confounding factors in the grade data that needed to be considered, and a review of the initial draft of this in-depth critical assessment of the authors' paper.

## "FOOTNOTES

Accepted Feb 15, 2006.

Address correspondence to Eric Fombonne, MD, Montréal Children's Hospital, 4018 Ste-Catherine West, Montreal, Quebec, Canada H3Z 1P2. E-mail: eric.fombonne@mcgill.ca"

[**Note:** Dr. Eric Fombonne, Director of Child Psychiatry for MUHC, Montreal Children's Hospital Psychiatry, Department of, Telephone: 1-514-412-4449 loc. 22174]

"In the United Kingdom, Dr Fombonne has provided advice on the epidemiology and clinical aspects of autism to scientists advising parents, to vaccine manufacturers, and to several government committees between 1998 and 2001. Since June 2004, Dr Fombonne has been an expert witness for vaccine manufacturers in US thimerosal litigation. None of his research has ever been funded by the industry."

Please address correspondence to Paul G. King, PhD, 33 Hoffman Avenue, Lake Hiawatha, NJ 07034-1922 USA. Email: drking@gti.net.

In the United States and The Peoples Republic of China, Dr. King has long provided compensated and, in some cases, *pro bono*, advice on chemistry, pharmaceutics, and regulatory compliance as well as, when requested, providing consulting and training to pharmaceutical companies as well as at cost training and *pro bono* advice to the US FDA in the areas of representative sampling, compound purity assessment, specific identity assessment, sample and population statistics, quality systems, and CGMP compliance *minimums*.

From the United States, Dr. King has provided in-depth assessments of papers addressing the causeless "autism" disorder and other "causeless" neurodevelopmental, psychological disorders, the effectiveness and safety of vaccines and other biological products containing Thimerosal, and the subacute mercury poisoning of humans and animals.

Since 1999, Dr. King has been engaged in the study of the published research in which some form of mercury may be a key factor in the papers that have directly or indirectly assessed the effects of mercury or its inorganic or organic compounds on humans, animals, cells and fundamental biochemical processes.

In addition, he has commented on many FDA guidances, is the lead author of the Citizen Petition filed with the FDA in docket 2004P-0349, has drafted legislation for the removal of all mercury-containing drugs from the market and the banning of the use of mercury in medical and dental procedures, has provided chain-of-custody protocols for use in the controlled testing of Thimerosal-containing drug products, written legislation designed to return the FDA to an effective agency whose only mission is to protect the public, and generated detailed legislation designed to truly improve the National Vaccine Injury Compensation Program.

None of these activities have been funded by any part of the healthcare establishment or by any activist, governmental, or public-interest group.

## "TABLES:

**TABLE 1** Gender and Age Distribution by PDD Diagnostic Subtypes

| Variable | Autism ($N = 61$), $n$ (%)[a] [21.98][b] | PDDNOS ($N = 91$), $n$ (%) [32.79] | Asperger ($N = 28$), $n$ (%) [10.09] | All PDD ($N = 180$), $n$ (%) [64.87] | $P$ |
|---|---|---|---|---|---|
| Male | 51 (83.6) | 79 (86.8) | 19 (67.9) | 149 (82.8) | .066 |
| Age, y | | | | | |
| 5–7 | 30 (49.2) | 17 (18.7) | 2 (7.1) | 49 (27.2) | |
| 8–10 | 13 (21.3) | 44 (48.4) | 10 (35.7) | 67 (37.2) | <.001 |
| 11–13 | 10 (16.4) | 21 (23.1) | 7 (25.0) | 38 (21.1) | |
| ≥14 | 8 (13.1) | 9 (9.9) | 9 (32.1) | 26 (14.4) | |

[a] The subject with CDD has been included in the autism group. "

[b] The numbers in brackets are this reviewer's computed incidence rates per 10,000 students based on the text's 27,749 registered students; autism value does *not* match authors' reported value of 21.6.

"**FIGURES:**

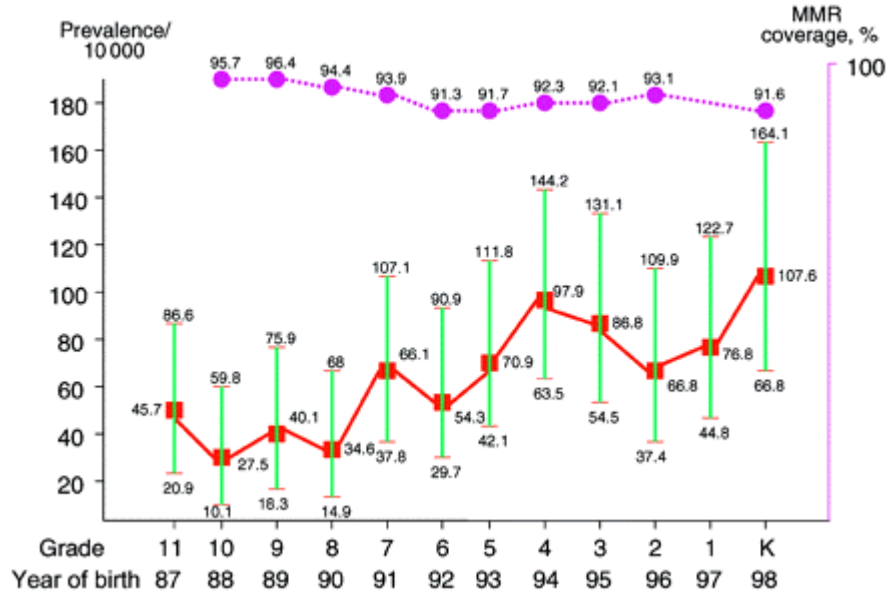



**FIGURE 1** MMR vaccine coverage and PDD rates over time. "

[**Note:** The left-hand "Y-axis" label should have been "Incidence/10000" instead of "*Prevalence/10000*".]

"

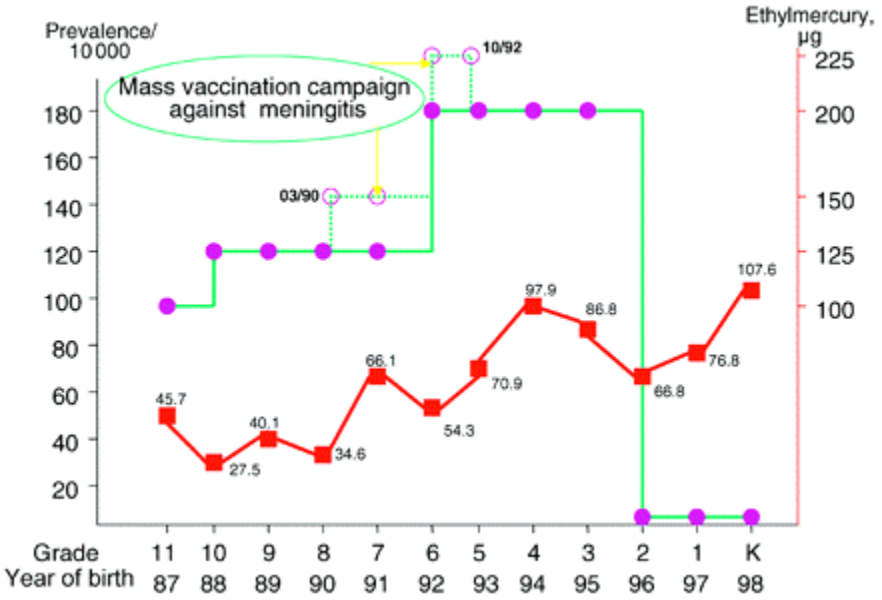



**FIGURE 2** Birth cohort prevalence rates and ethylmercury exposure. Dotted lines take into account the additional ethylmercury exposure because of a mass vaccination campaign against meningitis (see text)."

[**Note:** The left-hand "Y-axis" label should have been "Incidence/10000" instead of "*Prevalence/10000*" and "***FIGURE 2***" legend "*Birth cohort prevalence ...*" should be "*Birth cohort*" incidence ...".]

## "REFERENCES


1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 4th ed. Washington, DC: American Psychiatric Association; 1994
2. Muhle R, Trentacoste SV, Rapin I. The genetics of autism. Pediatrics. 2004;(113). Available at: www.pediatrics.org/cgi/content/full/113/5/e472
3. National Research Council. Educating Children With Autism. Washington, DC: National Academy Press; 2001
4. Smith T, Groen AD, Wynn JW. Randomized trial of intensive early intervention for children with pervasive developmental disorder. Am J Ment Retard. 2000;105 :269 –285[CrossRef][ISI][Medline]
5. Howlin P, Goode S, Hutton J, Rutter M. Adult outcome for children with autism. J Child Psychol Psychiatry. 2004;45 :212 –229[CrossRef][Medline]
6. Fombonne E. Epidemiological surveys of autism and other pervasive developmental disorders: an update. J Autism Dev Disorder. 2003a;33 :365 –382[CrossRef][ISI][Medline]
7. Fombonne E. Epidemiological studies of autism and pervasive developmental disorders. In: Volkmar F, ed. Handbook of Autism and Pervasive Developmental Disorders. 3rd ed. New York, NY: Wiley & Sons; 2005:42–69
8. Chakrabarti S, Fombonne E. Pervasive developmental disorders in preschool children. JAMA. 2001;285 :3093 –3099[Abstract/Free Full Text]
9. Chakrabarti S, Fombonne E. Pervasive developmental disorders in preschool children: confirmation of high prevalence. Am J Psychiatry. 2005;162 :1133 –1141[Abstract/Free Full Text]
10. Fombonne E. The prevalence of autism. JAMA. 2003;289 :1 –3[CrossRef]
11. Fombonne E. Is there an epidemic of autism? Pediatrics. 2001;107 :411 –413[Free Full Text]
12. Gernsbacher MA, Dawson M, Goldsmith HH. Three reasons not to believe in an autism epidemic. Curr Dir Psychol Sci. 2005;14 :55 –58[CrossRef][ISI]
13. Barbaresi WJ, Katusic SK, Colligan RC, Weaver AL, Jacobsen SJ. The incidence of autism in Olmsted County, Minnesota, 1976–1997: results from a population-based study. Arch Pediatr Adolesc Med. 2005;159 :37 –44[Abstract/Free Full Text]
14. Gurney JG, Fritz MS, Ness KK, Sievers P, Newschaffer CJ, Shapiro EG. Analysis of prevalence trends of autism spectrum disorder in Minnesota. Arch Pediatr Adolesc Med. 2003;157 :622 –627[Abstract/Free Full Text]
15. Newschaffer CJ, Falb MD, Gurney JG. National autism prevalence trends from United States special education data. Pediatrics. 2005;115 (3). Available at: www.pediatrics.org/cgi/content/full/115/3/e277
16. Arndt TL, Stodgell CJ, Rodier PM. The teratology of autism. Int J Dev Neurosci. 2005;23 :189 –199[CrossRef][ISI][Medline]
17. Wakefield A, Murch S, Anthony A, et al. Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children. Lancet. 1998;351 :637 –641[CrossRef][ISI][Medline]
18. Madsen KM, Hviid A, Vestergaard M, et al. A population-based study of measles, mumps, and rubella vaccination and autism. N Engl J Med. 2002;347 :1477 –1482[Abstract/Free Full Text]
19. Smeeth L, Cook C, Fombonne E, et al. MMR vaccination and pervasive developmental disorders: a case-control study. Lancet. 2004;364 :963 –969[CrossRef][ISI][Medline]
20. DeStefano F, Bhasin TK, Thompson WW, Yeargin-Allsopp M, Boyle C. Age at first measles-mumps-rubella vaccination in children with autism and school-matched control subjects: a population-based study in metropolitan Atlanta. Pediatrics. 2004;113 :259 –266[Abstract/Free Full Text]
21. Chen W, Landau S, Sham P, Fombonne E. No evidence for links between autism, MMR and measles virus. Psychol Med. 2004;34 :543 –553[CrossRef][ISI][Medline]
22. Dales L, Hammer S, Smith N. Time trends in autism and MMR immunization coverage in California. JAMA. 2001;285 :1183 –1185[Abstract/Free Full Text]
23. Taylor B, Miller E, Farrington C, et al. Autism and measles, mumps, and rubella vaccine: no epidemiological evidence for a causal association. Lancet. 1999:353 :2026 –2029[CrossRef][ISI][Medline]
24. Fombonne E, Chakrabarti S. No evidence for a new variant of measles-mumps-rubella-induced autism. Pediatrics. 2001;108(4). Available at: www.pediatrics.org/cgi/content/full/108/4/e58
25. Institute of Medicine. Immunization Safety Review: Vaccines and Autism. Washington, DC: National Academies Press; 2004
26. Demicheli V, Jefferson T, Rivetti A, Price D. Vaccines for measles, mumps and rubella in children. Cochrane Database Syst Rev. 2005;(4):CD004407

27. Jansen VA, Stollenwerk N, Jensen HJ, Ramsay ME, Edmunds WJ, Rhodes CJ. Measles outbreaks in a population with declining vaccine uptake. Science. 2003;301 :804[Free Full Text]
28. Ball L, Ball R, Pratt D. An assessment of thimerosal use in childhood vaccines. Pediatrics. 2001;107 :1147 –1154[Abstract/Free Full Text]
29. Halsey NA, Hyman SL, Conference Writing P. Measles-mumps-rubella vaccine and autistic spectrum disorder: report from the New Challenges in Childhood Immunizations Conference convened in Oak Brook, Illinois, June 12–13, 2000. Pediatrics. 2001;107 (5). Available at: www.pediatrics.org/cgi/content/full/107/5/e84
30. Andrews N, Miller E, Grant A, Stowe J, Osborne V, Taylor B. Thimerosal exposure in infants and developmental disorders: a retrospective cohort study in the United kingdom does not support a causal association. Pediatrics. 2004;114 :584 –591[Abstract/Free Full Text]
31. Heron J, Golding J. Thimerosal exposure in infants and developmental disorders: a prospective cohort study in the United Kingdom does not support a causal association. Pediatrics. 2004;114 :577 –583[Abstract/Free Full Text]
32. Hviid A, Stellfeld M, Wohlfahrt J, Melbye M. Association between thimerosal-containing vaccine and autism. JAMA. 2003;290 :1763 –1766[Abstract/Free Full Text]
33. Verstraeten T, Davis RL, DeStefano F, et al. Safety of thimerosal-containing vaccines: a two-phased study of computerized health maintenance organization databases. Pediatrics. 2003;112 :1039 –1048[Abstract/Free Full Text]
34. Madsen KM, Lauritsen MB, Pedersen CB, et al. Thimerosal and the occurrence of autism: negative ecological evidence from Danish population-based data. Pediatrics. 2003;112 :604 –606[Abstract/Free Full Text]
35. Stehr-Green P, Tull P, Stellfeld M, Mortenson PB, Simpson D. Autism and thimerosal-containing vaccines: lack of consistent evidence for an association. Am J Prev Med. 2003;25 :101 –106[CrossRef][ISI][Medline]
36. Geier DA, Geier MR. Thimerosal in childhood vaccines, neurodevelopmental disorders, and heart disease in the United States. J Am Phys Surg. 2003;8 :6 –11
37. Geier DA, Geier MR. An assessment of the impact of thimerosal on childhood neurodevelopmental disorders. Pediatr Rehabil. 2003;6 :97 –102[CrossRef][Medline]
38. Parker SK, Schwartz B, Todd J, Pickering LK. Thimerosal-containing vaccines and autistic spectrum disorder: a critical review of published original data. Pediatrics. 2004;114 :793 –804[Abstract/Free Full Text]
39. Ip P, Wong V, Ho M, Lee J, Wong W. Mercury exposure in children with autistic spectrum disorder: case-control study. J Child Neurol. 2004;19 :431 –434[ISI][Medline]
40. Pichichero ME, Cernichiari E, Lopreiato J, Treanor J. Mercury concentrations and metabolism in infants receiving vaccines containing thiomersal: a descriptive study. Lancet. 2002;360 :1737 –1741[CrossRef][ISI][Medline]
41. Kennedy RF Jr. Deadly immunity. Available at: www.rollingstone.com/politics/story. Accessed June 20, 2005
42. Kirby D. Evidence of Harm: Mercury in Vaccines and the Autism Epidemic—A Medical Controversy. New York, NY: St. Martin's Press; 2005
43. Associated Press. Boy with autism dies after chelation therapy. Available at: www.msnbc.msn.com/id/9074208. Accessed May 12, 2006
44. Bryson SE, Clark BS, Smith IM. First report of a Canadian epidemiological study of autistic syndromes. J Child Psychol Psychiatry. 1998;4 :433 –445
45. Ministère de la Santé et des Services Sociaux du Québec. Protocole d'immunisation du Québec. 1st ed. 2nd revision. Ministère de la Santé et des Services Sociaux du Québec; 1992
46. Ministère de la Santé et des Services Sociaux du Québec. Protocole d'immunisation du Québec. Québec, Canada: Ministère de la Santé et des Services Sociaux du Québec; 1995
47. Ministère de la Santé et des Services Sociaux du Québec. Protocole d'immunisation du Québec. 2nd ed, avril 1995, ainsi que ses mises à jour décembre 1995 et octobre. Québec, Canada: Ministère de la Santé et des Services Sociaux du Québec; 1997
48. Ministère de la Santé et des Services Sociaux du Québec. Protocole d'immunisation du Québec. 4th ed, avril 1999, ainsi que ses mises à jour avril; Québec, Canada: Ministère de la Santé et des Services Sociaux du Québec; 2002
49. Ministère de la Santé et des Services Sociaux du Québec. Protocole d'immunisation du Québec. 5th ed, avril 2004, ainsi que ses mises à jour septembre et novembre 2004. Available at: www.msss.gouv.qc.ca/sujets/santepub/preventioncontrole/immunisation/fs_immunisation.html. Accessed January 30, 2006
50. Hudson P, Allard R, Joseph L, Valiquette L. Vaccine coverage of 2-year-old children in Montreal, 2003. Communication at the 6th Canadian Immunization Conference; December 5–8, 2004; Montreal, Quebec, Canada

51. Charbonneau S, Riou D, Grignon R. Enquête vaccinale auprès des enfants de 2–2 ans du territoire du DSC Cité de la Santé de Laval. Laval, Québec, Canada: Département de Santé Communautaire; 1987:51
52. Landry M, Valiquette L, Allard R, Cionti M, Chrétien S. Enquête sur la couverture vaccinale des enfants de 24–30 mois. DSC Cité de la Santé de Laval et DSC Maisonneuve-Rosemont; Presented at: the 3rd Quebec Colloquium of Infectious Disease; Quebec, Canada; November 1992
53. Lafontaine G, Sauvageau Y. Couverture vaccinale des enfants agés de 2 ans du territoire du DSC de l'Hopital Charles Lemoyne. Quebec, Canada: Département de Santé Communautaire de l'Hopital Charles Lemoyne; 1990:36
54. Marin-Lira A, Soto JC. Un regard aux études sur la couverture vaccinale au Québec. Document de travail. Québec, Canada: Direction de la Santé Publique de Laval; 1996:24
55. De Wals P, De Serres G et Niyonsenga T. Effectiveness of a Mass immunization campaign against serogroup C meningococcal disease in Quebec. JAMA. 2001;285 :177 –181[Abstract/Free Full Text]
56. SAS Institute. SAS/STST User's Guide, Version 6. 4th ed. Vol 2. Cary, NC: SAS Institute; 1990
57. Allison P. Logistic regression using the SAS system: theory and application. Cary, NC: SAS Institute Inc and John Wiley; 2001
58. World Health Organization. The ICD-10 Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostic Guidelines. Geneva, Switzerland: World Health Organization; 1992
59. Kielinen M, Linna S-L, Moilanen I. Autism in Northern Finland. Eur Child Adolesc Psychiatr. 2000;9 :162 –167[CrossRef][ISI][Medline]
60. Direction de l'adaptation scolaire et des services complementaires. Students With Handicaps, Social Maladjustments, or Learning Difficulties: Definitions. Gouvernement duq Uébec. Ministere de l'Education, 2000-00-0078. Quebec, Canada: Bibliotheque Nationale duq Uébec; 2000
61. Croen LA, Grether JK, Hoogstrate J, Selvin S. The changing prevalence of autism in California. J Autism Dev Disord. 2002;32 :207 –215[CrossRef][ISI][Medline]
62. Laidler JR. US Department of Education data on "autism" are not reliable for tracking autism prevalence. Pediatrics. 2005;116 :120 –124[CrossRef]
63. Smeeth L, Rodrigues LC, Hall AJ, Fombonne E, Smith PG. Evaluation of adverse effects of vaccines: the case-control approach. Vaccine. 2002;20 :2611 –2617[CrossRef][ISI][Medline]
64. Jick H, Kaye JA. Autism and DPT vaccination in the United Kingdom. N Engl J Med. 2004;350 :2722 –2723[Free Full Text]
65. Bertrand J, Mars A, Boyle C, Bove F, Yeargin-Allsopp M, Decoufle P. Prevalence of autism in a United States population: the Brick Township, New Jersey, investigation. Pediatrics. 2001;108 :1155 –1161[Abstract/Free Full Text]
66. Honda H, Shimizu Y, Rutter M. No effect of MMR withdrawal on the incidence of autism: a total population study. J Child Psychol Psychiatry. 2005;46 :572 –579[Medline]
67. Gillberg C, Heijbel H. MMR and autism. Autism. 1998;2 :423 –424[CrossRef]
68. Lord C, Shulman C, DiLavore P. Regression and word loss in autistic spectrum disorders. J Child Psychol Psychiatry. 2004;45 :936 –955[Medline]
69. Taylor B, Miller E, Lingam R, Andrews N, Simmons A, Stowe J. Measles, mumps, and rubella vaccination and bowel problems or developmental regression in children with autism: population study. BMJ. 2002;324 :393 –396[Abstract/Free Full Text]
70. Fombonne E, Heavey L, Smeeth L, et al. Validation of the diagnosis of autism in general practitioner records. BMC Public Health. 2004;4 :5[CrossRef][Medline]
71. Salmon DA, Haber M, Gangarosa EJ, Phillips L, Smith NJ, Chen RT. Health consequences of religious and philosophical exemptions from immunization laws: individual and societal risk of measles. JAMA. 1999;282 :47 –53[Abstract/Free Full Text]
72. McBrien J, Murphy J, Gill D, Cronin M, O'Donovan C, Cafferkey MT. Measles outbreak in Dublin, 2000. Pediatr Infect Dis J. 2003;22 :580 –584[CrossRef][ISI][Medline]"